The Journal

OF THE KANSAS MEDICAL SOCIETY

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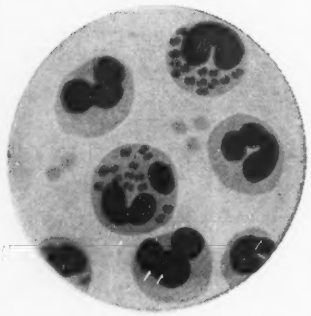

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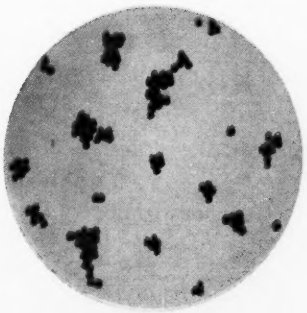

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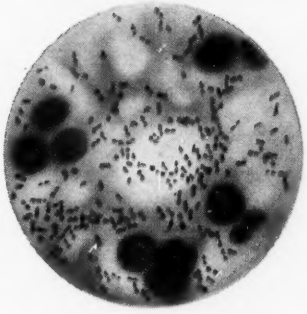

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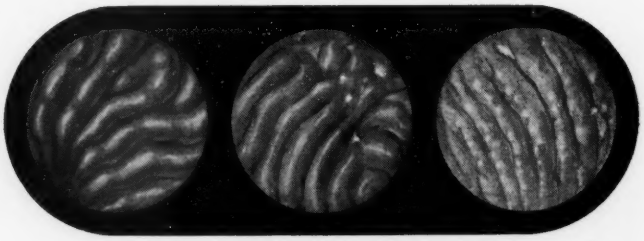

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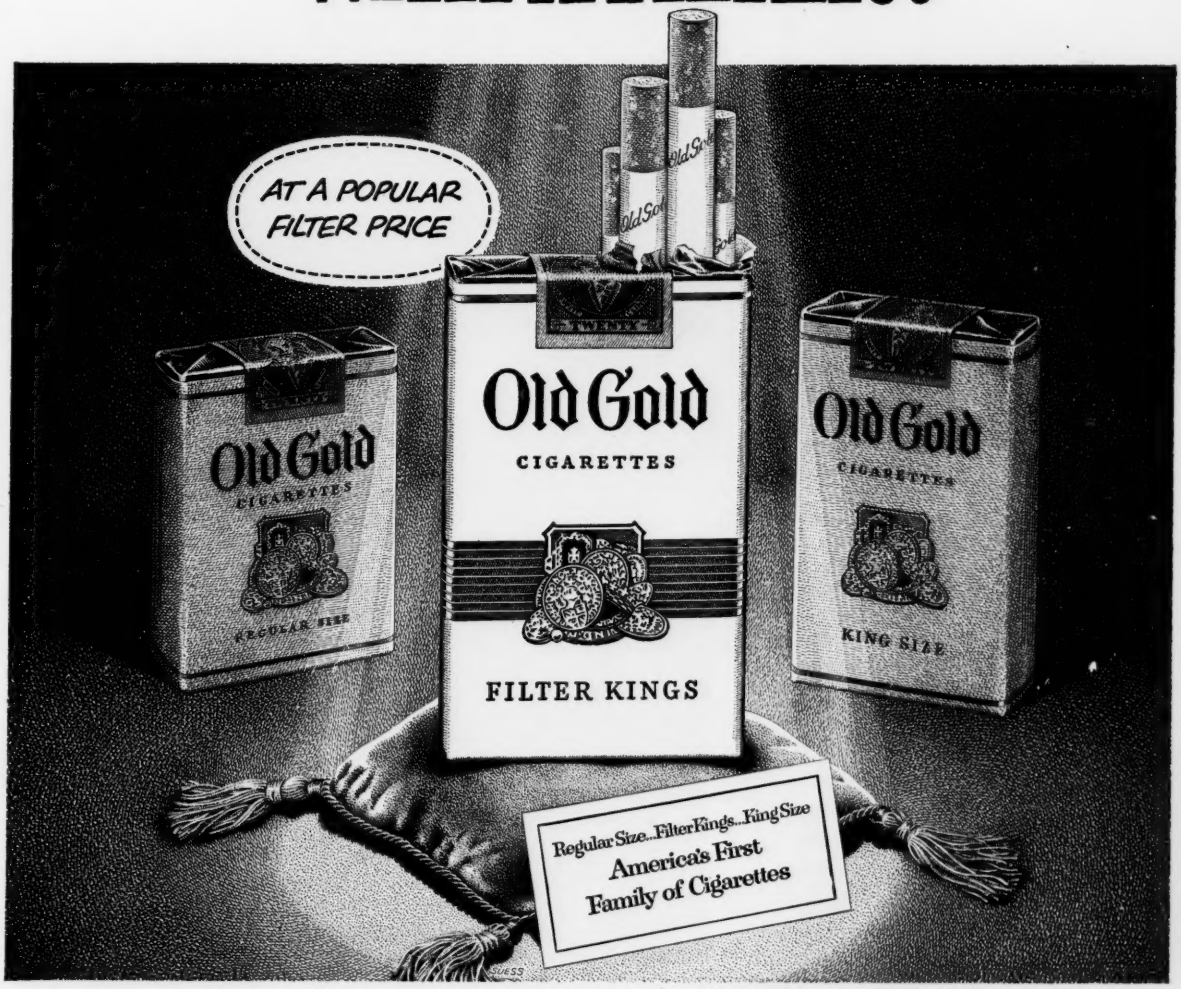

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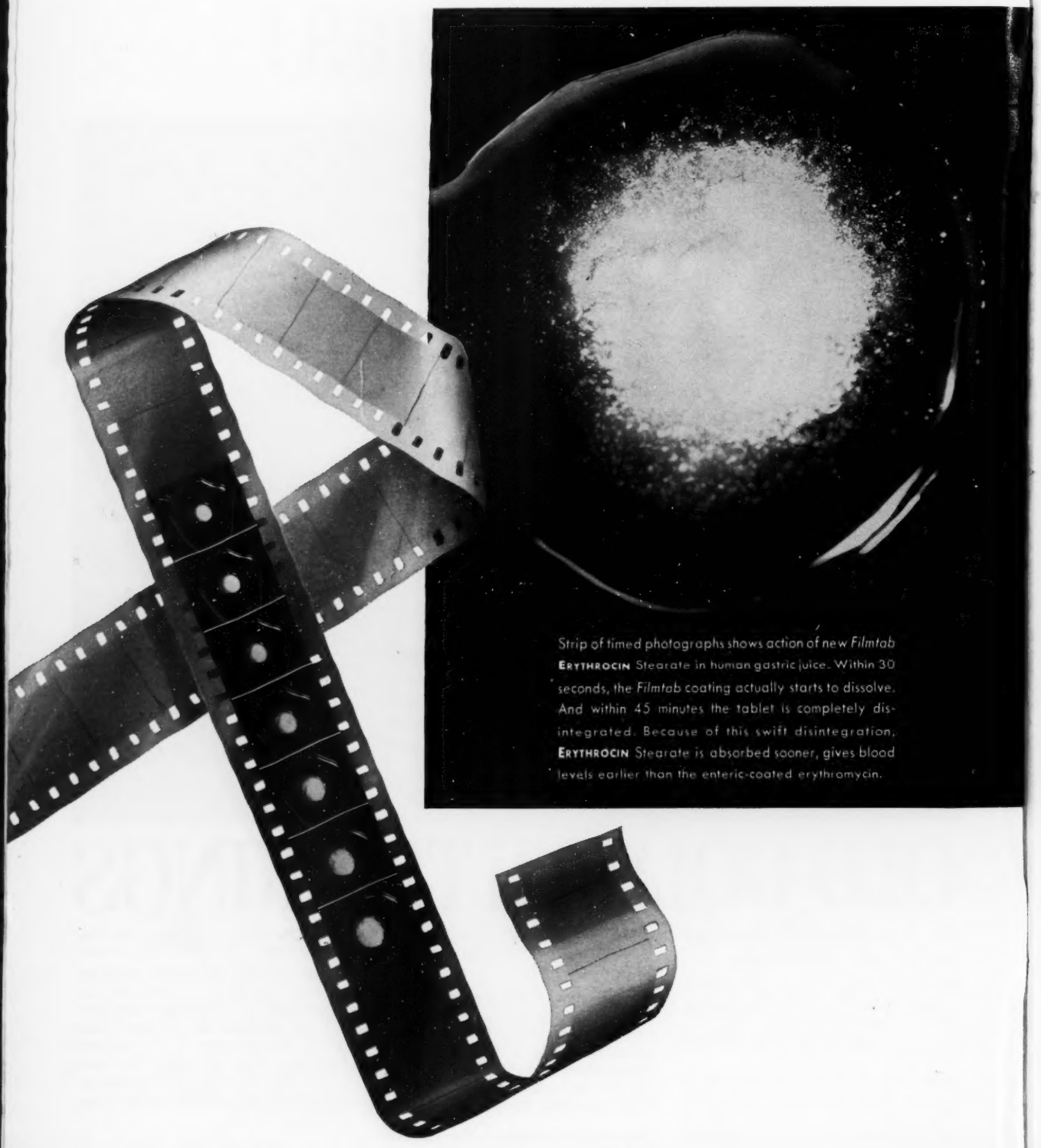

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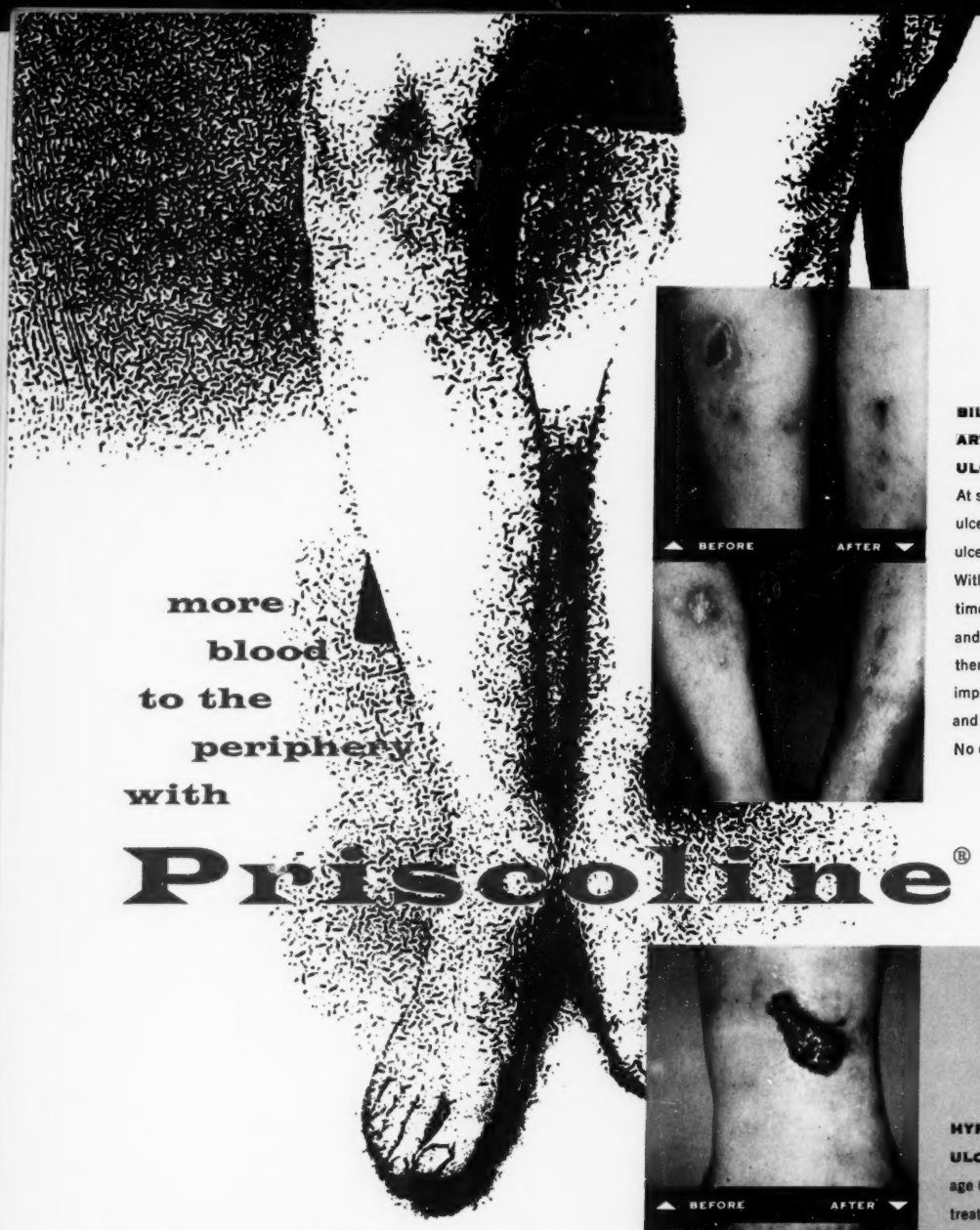

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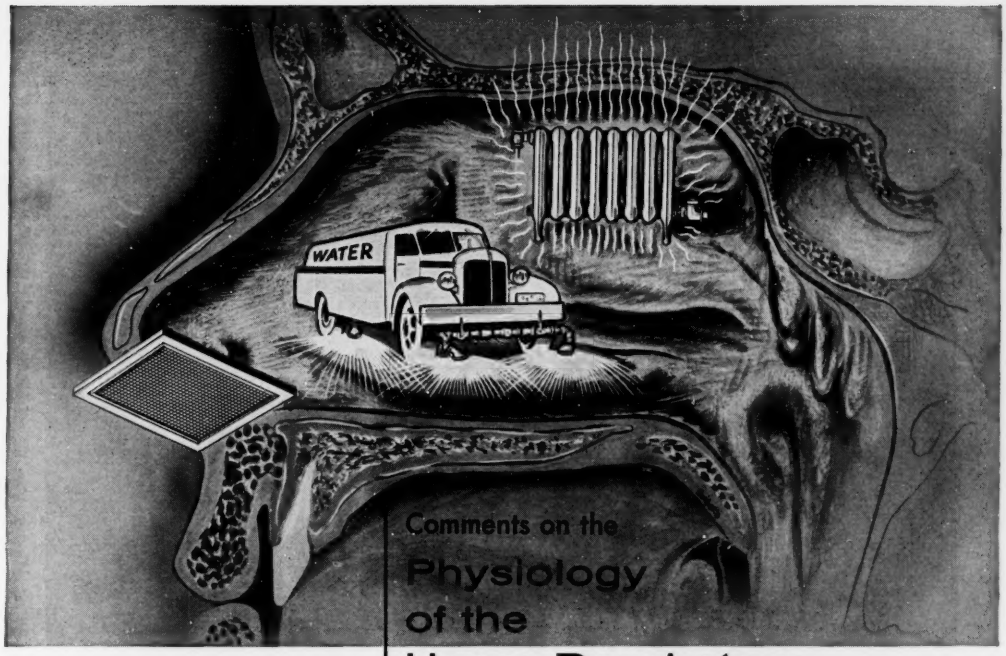

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Volume LV DECEMBER, 1954 No. 12

The Hypoprothrombinemia-Inducing Activity of Warfarin* Sodium (Coumadin® Sodium)

Shepard Shapiro, M.D.
New York, New York

It is possible to prevent or limit thrombosis and thrombo-embolism by rendering the blood hypocoagulable. To achieve this there are available two types of clotting inhibitors: (1) heparin and heparinoid substances which extend the whole blood coagulation and (2) bishydroxycoumarin (Dicumarol®) and similar agents which reduce the level or activity of plasma prothrombin. Heparin was introduced for clinical use in the middle 30's by Swedish and Canadian investigators,[1] and the 4-hydroxycoumarin drug was discovered at the University of Wisconsin by Professor Karl Paul Link and his students in 1939.[2] This paper deals only with 4-hydroxycoumarin compounds.

In the treatment of acute thrombotic disorders the immediate goal is to prevent extension of intravascular clotting and to avoid liberation of emboli from the thrombotic mass. As has been indicated, this can be accomplished by rendering the blood hypocoagulable, and if a 4-hydroxycoumarin drug is used a satisfactory clinical response can usually be achieved by prolonging the prothrombin time as estimated by the single-stage method to the range of "therapeutic" hypoprothrombinemia.

It has been universal experience that certain difficulties have been encountered when Dicumarol® or a related compound has been employed. The hypoprothrombinemia response may be uncertain and irregular in onset, intensity, and duration. These drugs are all administered orally, and variability of absorption from the digestive tract has been a contributory factor. Because of these facts more desirable compounds have been sought.

Several years ago I pointed out that a desirable anticoagulant should possess a high degree of therapeutic activity, be completely and promptly absorbed, exhibit predictable response with early onset of effectiveness and minimum hazard of hemorrhage, and be without other adverse effects.

The purpose of this paper is to describe a new and more dependable drug for the therapy of thrombotic and thromboembolic disorders. It is a 4-hydroxycoumarin compound which possesses the desirable characteristics described above more than any related drug in current use.

After Professor Link and his co-workers isolated Dicumarol®, they screened many analogues for their hypoprothrombinemia-inducing activity. As a by-product of this investigation, one compound, Warfarin (3 (α-acetonyl benzyl)-4 hydroxycoumarin) was recommended by Professor Link for rodent control. It was found that the hypoprothrombinemia observed in various experimental animals with a given dose of Warfarin was generally more reproducible than that induced by Dicumarol® and that it was readily reversed by water-soluble preparations of menadione and by K_1. It was also noted that Warfarin exhibits greater potency and earlier onset of action than

* (3-(α-acetonyl benzyl)-4 hydroxycoumarin)

Presented at the annual meeting, Kansas Medical Society, Topeka, Kansas, May 5, 1954. Dr. Shapiro is assistant professor of clinical medicine, New York University College of Medicine.
Coumadin Sodium® was prepared by Dr. Samuel M. Gordon, Endo Products, Inc., Richmond Hill, New York.

the parent drug. Because of these facts I made clinical trials with the new drug in man.

Initial unpublished observations were dramatically confirmed by an accident reported by Holmes and Love[8] of a patient who took large doses of Warfarin in a suicide attempt on six successive days, greatly in excess of the therapeutic dose now employed safely in man. They confirmed that Warfarin was qualitatively identical with Dicumarol®, that it was highly susceptible to counteraction by menadione, and that it caused no adverse side effects. Only bleeding followed the excessive dosage.

On the basis of these data it was postulated that if Warfarin, which is insoluble, could be prepared in a form suitable for parenteral administration, it would be preferable to any of the drugs now in clinical use. A stable sodium salt of Dicumarol® cannot be made, and the same holds for cyclocumarol which cannot be converted into a sodium salt because of the fact that it has no free hydroxyl group. Warfarin was made available as the sodium salt, and Professor Link supplied me with this material. It possesses the following characteristics:

1. It is soluble in water.
2. It is effective intravenously, intramuscularly, or orally.
3. Relatively small doses are required to induce therapeutic hypoprothrombinemia.
4. Initial prolongation of prothrombin time occurs earlier than after Dicumarol®, cyclocumarol, or ethyl biscoumacetate (Tromexan®).
5. Its tendency to produce hemorrhage from overdosage is less than with the three 4-hydroxycoumarin drugs mentioned above.
6. It yields a smooth extended curve of hypoprothrombinemia in contrast to ethyl biscoumacetate which produces frequent fluctuations in prothrombin time.

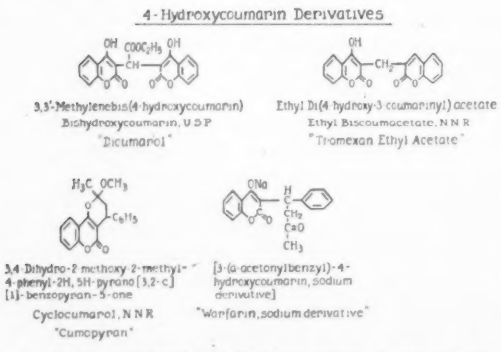

Figure 1. The relationship of Warfarin Sodium to bishydroxycoumarin, ethyl biscoumacetate, and cyclocumarol is illustrated in the above structural formulae. Warfarin Sodium is the sodium salt of the enol form. Stable water-soluble forms of the other 4-hydroxycoumarin anticoagulants illustrated above cannot be prepared.

7. Its effect upon the prothrombin time is readily counteracted by water-soluble menadione or by K_1.

The aqueous solution used by me contains 75 mg. in 2 ml. solution, suitable for intravenous or intramuscular administration. Scored tablets for oral use contain 25 mg. each. Absorption is equally effective by the three routes of administration. I prefer intravenous or intramuscular injection to initiate treatment and during the stages of active thrombosis or thrombo-embolism because it is then of the greatest importance that the blood be rendered and maintained hypocoagulable. After the acute stages have subsided therapy can be continued satisfactorily by oral administration. Therapy can be instituted effectively by mouth also, but for the reasons stated above injection is preferable. Dosages by all routes are at the same level and frequency.

The initial dose is 1 mg. per kilogram of body weight. The smallest starting dose, regardless of weight, is 50 mg., and patients weighing more than 75 kilos are given 100 mg. The new drug, like all other related compounds, must be controlled by reliable and properly spaced estimations of prothrombin time.

I prefer to administer doses by the intermittent method, to be described presently, regardless of the route used. Succeeding doses are given after the prothrombin time extended by the previous dose begins to fall from the highest point on the prothrombin curve. Subsequent doses after the first dose are two-thirds of the initial dose unless the prothrombin time has approximated normal, in which case the same dose first used is repeated. The mode of administration after the first dose is a matter of choice although spaced intravenous injections may be used according to the intermittent dosage schema. Parenteral doses may be given every four or five days, or the drug may be given orally with suitable attention to dose and frequency. If daily maintenance doses are desired, in contrast to the intermittent method, about 12.5 mg. per day or 25 mg. every other day, orally, is usually adequate to retain the prothrombin time of the whole plasma within the accepted therapeutic range of between 1½ and 2½ times normal in seconds, by the single stage method. For intermittent oral dosage I have found 50 mg. every third or fourth day, depending upon the patient's characteristics, usually suffices. Because of the regularity of response after Warfarin, it is usually possible to forecast subsequent doses after the prothrombin time curve for a given individual has been established.

The drug is well tolerated, and no side effects have been noted. Hemograms, liver function tests, and repeated urine analyses have revealed no adverse side reactions. As is true of all anticoagulants,

this drug may induce bleeding from ulcerated or necrotic tissues when the blood is rendered hypocoagulable. Before anticoagulants are administered, the clinician must satisfy himself concerning such risks. In general, however, experience has been that bleeding tendency, such as gross hematuria, has occurred less frequently with Warfarin Sodium than from Dicumarol®, cyclocumarol, and Tromexan®.

Excessive hypoprothrombinemia with or without bleeding induced by Warfarin Sodium is highly susceptible to correction by water-soluble menadione or K_1 emulsion. An added advantage is the fact that K_1 is effective in small dosage and (at least in the rare instances in which I have had to employ it) is not followed by the continuation of normal prothrombin time for many days even in spite of additional doses of anticoagulant. On the contrary, the prothrombin time promptly becomes extended after it recedes to normal. The importance of these phenomena in active thrombotic or thrombo-embolic disease is obvious (Figure 2).

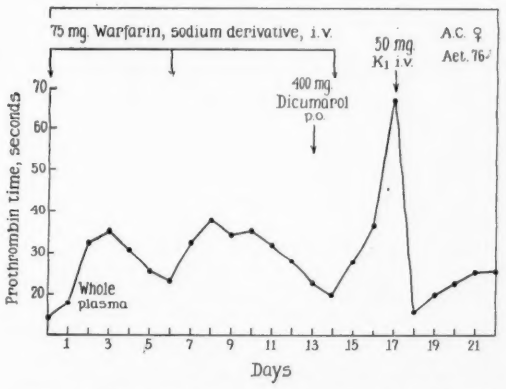

Figure 2. Illustrating excessive prolongation of prothrombin time and response to K1. During recovery phase after second dose, attempt was made to substitute Dicumarol, 400 mg. orally, on the 13th day. Failure or delayed absorption reflected in decrease in prothrombin time on 14th day, and 75 mg. Warfarin intravenously was given. Excessive prolongation to 67 seconds (normal 14 seconds) on 17th day and 50 mg. K1 (Merck) was administered intravenously. Fifteen hours later prothrombin time was 15.5 seconds followed by gradual increase to 17, 22, 25 and 25 seconds respectively on succeeding four days.

In the conduct of anticoagulant therapy the clinician must constantly be alert to the physiologic alterations inherent in the prothrombin producing mechanism. By virtue of this, some patients may be highly susceptible while others may be relatively resistant to the inhibitory agent. It is imperative, therefore, that the therapy be controlled by reliable estimation of prothrombin time. The high order of predictability of response after Warfarin following the establishment of the pattern of prolonged prothrombin time after a given dose and the regularity of this response should place the management of thrombotic and thrombo-embolic disorders with the new drug on a more certain plane than has prevailed to the present.

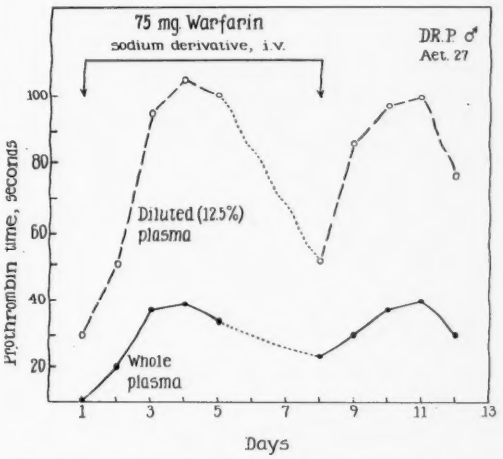

Figure 3. Illustrating intermittent doses and regularity of response after 75 mg. Warfarin Sodium was given on 1st day and 8th day. Note plateau at therapeutic level after each dose lasting three days and selection of points on curve when prothrombin time estimations (6th and 7th days) can be safely omitted.

The therapeutic efficacy of an anticoagulant drug is determined by the facility with which it renders the blood hypocoagulable and maintains the state of reduced coagulability. Since the objective of inducing hypoprothrombinemia is for its favorable influence upon thrombosis and embolism, it is essential not only to induce adequate hypoprothrombinemia initially but also to continue hypocoagulability for the desired period of therapy. The susceptibility to further thrombosis in a patient who already has sustained a thrombotic episode can be overcome by inducing and continuing a state of hypocoagulability.

While the doses given above are recommended on the basis of clinical experience with the drug, it must be borne in mind that each patient responds according to his own individual characteristics. Fortunately the majority of persons react according to a pattern after Warfarin, although there are some persons who exhibit excessive responses while others are relatively resistant. It is because of this that there must always be individualization of dosage determined by the response pattern after the initial doses used. I pointed this out in the first symposium on Dicumarol® held in Atlantic City in 1942. This advice is no less true today than it was at that time. As I see it, if this point of view had been more generally accepted, there would have been less cause for alarm from induced hemorrhage from any of these drugs.

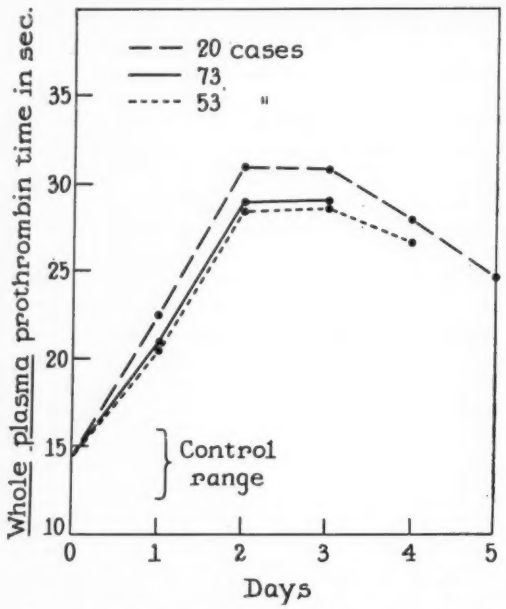

Figure 4. Illustrating mean responses in 20, 53, and total 73 cases respectively. Shows regularity and predictability of response pattern, all 3 curves being statistically practically superimposable.

Generally it is adequate for therapeutic purposes to prolong the prothrombin time of the whole plasma to between 1½ and 2½ times normal in seconds as determined by the Link-Shapiro modification of the Quick one-stage method. A normal of 15 seconds has been reliable in my hands, although a few workers prefer a normal of less than 15 seconds. In any event, constancy and reproducibility of the method employed are essential for the proper adjustment of dosage.

The accepted therapeutic range stated above is not infallible. Why some subjects exhibit rethrombosis when the prothrombin time is within the accepted therapeutic range is a subject for conjecture. When such events occur the clinician must re-evaluate the problem in the framework of the known phenomena, including the technic used for estimating prothrombin time.

It must be borne in mind that intravascular thrombosis represents the culmination of the interplay of a number of factors which need not be identical in every case and in which the state of the coagulability of blood usually represents the common denominator. It is because of this that rendering the blood hypocoagulable favorably influences thrombosis and thrombo-embolism. However, if the activity of other contributory causes becomes overwhelming they might counterbalance the limiting effects of hypocoagulability and, under such conditions, it is conceivable that the therapeutic efficacy of anticoagulants might be inadequate. Outstanding examples of this are cases of coronary artery thrombosis in which the closure of the vessel by dynamic obstructive sclerosis and spasm is so complete that anticoagulation is inadequate to alter the mechanism. Similarly, the thrombotic complications of sickle cell disease crises cannot be altered by rendering the blood non-coagulable.[4]

During the stages of active thrombosis or embolism I prefer to prolong the prothrombin time to the fullest therapeutic extent rather than to err on the side of inadequate dosage. Physiologically this is sound and clinically it is safe, particularly with Warfarin Sodium because of its ready reversibility by Vitamin K. Experience has shown that the incidence of bleeding following initially induced hypoprothrombinemia is relatively low as compared with that occurring when the prothrombin time has been maintained within a constant therapeutic range for an extended period. Why this is so is a subject for conjecture. Just as thrombosis is a multifaceted reaction, so is bleeding after overdosage a reflection of a combination of changes of which hypocoagulability is only one.

Another and essential element is, for want of a

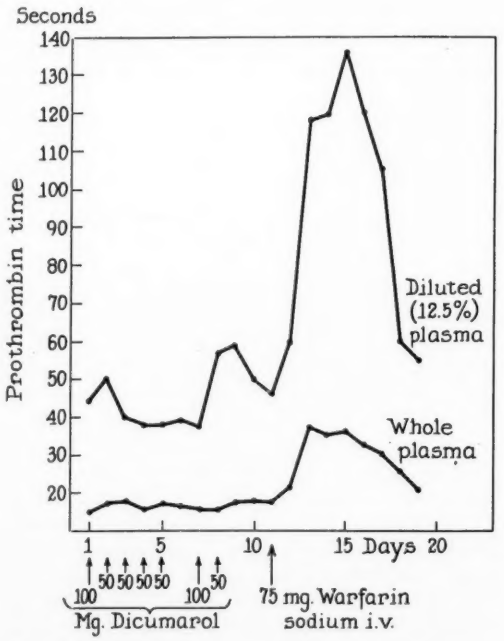

Figure 5. Illustrating the advantage of intravenous administration of Coumadin Sodium versus oral Dicumarol. Inadequate response in the case of a referred patient receiving "maintenance" doses of Dicumarol. On the 7th day pulmonary embolism occurred in spite of additional Dicumarol. On the 11th day, 75 mg. of Coumadin Sodium, given intravenously, induced a satisfactory therapeutic hypoprothrombinemia with cessation of emboli and followed by prompt recovery.

better description, identified as the integrity of the vascular wall. That this is real and how it is influenced can be appreciated from later remarks in this paper. They indicate that continued maintenance of hypocoagulability may impair the vascular wall integrity, which in turn may eventuate in hemorrhage whilst intermittent rise and fall of the level of coagulability permits the vascular wall to remain in a more normal state of integrity with avoidance of bleeding.

The genesis of the intermittent method may be of interest as it relates observations in animals to use in man. Early in 1940, while visiting Professor Link at the University of Wisconsin, I was shown two groups of dogs being treated experimentally with Dicumarol®. One group was given the drug daily; the other group was given equivalent quantities at intermittent intervals. After a while spontaneous hemorrhage occurred in the first group, but no bleeding occurred in the second series of dogs although the prothrombin time was substantially prolonged. These observations in dogs, plus the experience of farmers who found that those cattle ingesting spoiled sweet clover hay every day for many days contracted the hemorrhagic disease but those animals who received feed other than sweet clover hay intermittently did not manifest the hemorrhagic disorder, gave me the clue to the dosage schema which I established when I began to use Dicumarol® in man in 1940. Because of the relationship of these phenomena in dogs and cattle to those in man, I designated this the intermittent method. The essentials of the intermittent method are to give a relatively large initial dose and subsequent smaller doses after the prothrombin time has begun to recede from the peak prolongation of the prothrombin time from the previous dose.

This schema has made it possible to anticoagulate very sick patients for extended periods without serious hemorrhagic manifestations. This is in contrast to the so-called maintenance method in which daily or almost daily doses are given to keep the prothrombin time constantly within a fixed therapeutic range. The incidence of bleeding by this method has been substantially higher than with the intermittent method.

Warfarin Sodium parenterally and orally is particularly well suited for intermittent dosage therapy because its effect is initiated relatively early and continues within the accepted therapeutic range for several days after a single dose of therapeutic magnitude. The characteristics of the drug promise to simplify the management of thrombosis and embolism. This is one of the most serious problems confronting the clinician today since these disorders are most common in older age group patients now occupying the special attention of the profession.

SUMMARY

The foregoing may be summarized as follows:

1. A new hypoprothrombinemia-inducing agent has been described.
2. It can be given orally and, because its sodium derivative is highly soluble in water, its solution is suitable for intravenous or intramuscular administration.
3. Relatively small doses of the drug provide therapeutic hypoprothrombinemia.
4. It becomes effective earlier than the other 4-hydroxycoumarin anticoagulants.
5. It exhibits a low hemorrhage-producing tendency.
6. It causes no adverse side-effects. Only bleeding follows over-dosage, and this is readily corrected by water-soluble menadione and K_1.
7. It exhibits an almost uniformly smooth extended curve of hypoprothrombinemia.
8. It has a high predictability of prothrombin response.

The essentials and advantages of the intermittent method for which Warfarin Sodium is especially suited have been presented.

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Education is not merely the accumulation of facts or information. The process involves the assimilation of knowledge so that the learner becomes a different, a more effective, more useful and happier person than he would otherwise have been.

—Abbott Kaplan

Gallstone Ileus

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INTRODUCTION

Gallstone ileus is of the class of rare but too often highly fatal and missed diagnostic entities. Any surgeon or physician coping with acute abdominal cases in the older age patient should consider the probability of obstruction by gallstones in his résumé of pathological possibilities.

Its history is not new; in 1890 Courvoisier reported a series of such cases, and as early as 1654 Bartholin published a report of gallstones perforating into the small intestines. Von Wagoner analyzed a series of 334 cases in 1914, and Moore estimated in 1925 that about 400 cases of gallstone ileus had been reported at that time.

INCIDENCE

Gallstone ileus occurs most often in the older age patient between the seventh and eighth decades. It is most frequent in women giving histories of previous pregnancies and/or chronic digestive disturbances suggestive of biliary pathology or dysfunction.

A statistical incidence of gallstone ileus occurring in all cases of intestinal obstruction has been established, from a number of case study surveys, to range from 0.4 to 5 per cent with a figure of 1 to 2 per cent probably being more accurate.

MORTALITY

From an incidence percentage gallstone ileus would not seem too important, but mortality statistics speak otherwise. A surgical entity with a reported mortality range of 33 to 93 per cent, where such is preventable by early diagnosis and early adequate treatment, becomes a diagnostic possibility always to be remembered when dealing with intestinal obstruction in the elderly patient. Moore in 1924 found that the reported mortality of various authors ranged from 50 to 100 per cent. The present average mortality is still about 50 per cent.

PATHOGENESIS AND PATHOLOGY

Anatomically and pathologically, obstructive gallstones usually gain entrance to the intestinal tract initially by an abnormal communication between the biliary passages and the gut, such most often occurring between the gallbladder and duodenum. Wakefield, Vickers, and Walters[1] in their study of 152 cholecysto-enteric fistulae, representing 140 from the literature from 1922 to 1942 and 10 cases of their own, found a breakdown of 101 into the duodenum, 11 into the jejunum or ileum, 33 into the colon, and 7 into the stomach.

Rigler, Borgman, and Noble[2] feel that cases previously reported in which gallstones causing the intestinal obstruction had apparently passed through the ampulla of Vater had actually passed into the intestinal tract by way of a choledochoduodenal fistula near the end of the common duct. They present two cases in which such findings were seen at autopsy.

The etiological origin of such abnormal biliary intestinal tracts is still a matter of conjecture. Hinchey[3] feels such are resultant of obstruction of the common duct, and paradoxically these cholecysto or cholecystodocho-enteric fistulae are thus "life-saving" incidents. Coffey and Willox[4] are of the opinion that a cholecystitis with cholelithiasis must invariably precede the existence of a biliary intestinal tract fistula, causing a resultant inflammatory fixation of the gallbladder or portion of the biliary tree with eventual erosion into the adjacent bowel.

Fistulae arising from the biliary system do not always connect or empty into the gut. Multiple fistulae have been reported both at surgery and at autopsy and have varied in their communication from the biliary tract to the bronchial tree, renal pelvis, uterus, ovary, bladder, and pleural and pericardial cavities. Open fistulous tracts may not always be demonstrable at surgery, having often become partially or completely fibrosed from the time of original disease to the time of surgery or autopsy.

Fortunately most gallstones entering the gut are subsequently passed or vomited without causing serious obstructive symptoms. Gutman[5] estimates that fewer than one-half of all gallstones that pass into and through the gut cause obstruction.

Obstruction when present need not initially be on a mechanical basis alone. Wangensteen feels such may start as a paralytic or spastic ileus type caused by local irritation from a stone too small to block the gut lumen alone. Subsequently, with spastic reduction of the gut lumen, mechanical obstruction occurs. This mechanism could explain occurrence of intermittent obstruction in these patients; with reduction of spasm, the stone passes on until it becomes impacted again at a more distal site. It has been generally felt, as

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Barnard[7] stated, that stones must be 2½ centimeters or more in diameter to cause obstruction. Reduced gut lumen due to adhesions or scarring resulting from regional enteritis, diverticulitis, or other causes tends to obviate this dictum.

Obstructing gallstones have been found most frequently at the ileum. Courvoisier's[8] figures of 65.4 per cent in the ileum, 21.4 per cent in the duodenum or jejunum, 10 per cent at the ileocecal valve, and 2.4 per cent at the sigmoid flexure, are fairly accurate when compared with figures quoted by Foss and Summers,[9] who found out of 150 cases, 59 per cent having stones in the terminal ileum and 3.3 per cent in the colon or rectum. Understandably gallstones can conceivably lodge and have been reported as lodging in the appendix, Meckel's diverticulum, or other intestinal tract diverticula. Multiple stones may be present in the gut at any one time. In general it is felt that those stones entering the colon directly rarely cause obstruction and are usually passed with minimal or no difficulty.

Additionally, intestinal obstruction has been reported by Mayo, Robson, and Smith[10] as being due to volvulus caused by increased weight of the proximal loop from an accumulation of gas and fluid proximal to the gallstone. Rarely, although it has been reported by Wakefield, Vickers, and Walters,[1] obstruction can be caused by intussusception with the fixed gallstone as the point. The same authors report three cases of obstruction due to gallstone without the calculus actually being in the gut. In these cases the stone was lodged in the mesentery of the small gut, and a local abscess reaction caused subsequent development of intestinal obstruction.

Pressure ulceration and necrosis of the obstruction site and a perforation at the point of obstruction or above the point of obstruction, due to excess dilatation of the proximal loop, are pathological possibilities to be expected in the relatively late and often fatal cases.

CLINICAL FEATURES

Diagnosis of gallstone ileus is made by initially considering the possibility of this entity in an older age patient in the sixth or seventh decade presenting the clinical signs and symptoms of obstruction. A history suggestive of chronic dyspepsia or biliary pathology or dysfunction may or may not be elicited. Additionally there may be a history of previous intermittent partial or complete intestinal obstructions with fairly rapid recovery with or without conservative therapy. Dehydration, elevated nonprotein nitrogen, and blood chemistry imbalances are late findings. As with some cases of intestinal obstruction, gas and feces may be passed distal to the obstruction point, and such a finding should not mislead the physician.

X-ray is often diagnostic if the condition is kept in mind. To be looked for are roentgen findings of a partial or complete gut obstruction or ileus accompanied by the presence of gas in the biliary tract. Rigler, Borgman, and Noble[2] report gas seen in the biliary tree in the preoperative films in 13 out of 14 cases of gallstone ileus. They recommend that in consideration of such cases an anteroposterior or posteroanterior film centered over the right upper quadrant is best for visualization of gas or contrast media in the biliary tract. The finding of gas in the biliary passages is seen in only one other condition, an infection of the biliary area with a gas-forming organism.

Failure to visualize gas in the biliary tree even after repeated studies may be explained, as has been previously noted, by the fact that many of these biliary fistulae tend in time to close off by fibrosis. Additionally in the x-ray diagnostic surveys, where gallstones have been seen in previous films, any change in their positions should be sought and noted. Obviously x-rays will often help locate the site of obstruction, although distention of gut loops may be minimal or absent in those cases where obstruction is so often characteristically intermittent.

Right and left lateral decubitus views and supine and upright position x-rays of the abdomen are usually sufficient although, as noted before, close up views of the right upper quadrant area may be additionally helpful. Root[11] points out that pre-x-ray preparation with enemas or laxatives is not advisable; laxatives are omitted for obvious reasons and enemas because confusing air or fluid shadows may be introduced, thus obstructing diagnostic efforts rather than aiding such. Root has suggested using, and has used himself in questionable cases, a thin barium mix either swallowed or passed by way of a Miller-Abbott tube for localizing the points of obstruction. He introduces 20 to 30 cc. of such a mixture and uses both fluoroscopic examination and survey films. By this means, outlining of non-opaque stones should be possible. Barium enemas have been used more often and more acceptably for equivalent purposes.

DIFFERENTIAL DIAGNOSIS

Acute gastrointestinal obstruction from any cause in the older age patient is to be considered in the differential diagnosis when the gallstone ileus patient is first seen. Determination of previous abdominal surgery will aid in ruling in or out the common possibility of obstruction by adhesions. Absence of a history of chronic weight loss and anemia would tend to diminish the possibility of neoplasm. Enterocolitis with its intermittent symptoms may often be confusing, but a febrile response and an elevated white count are more often presented with this condition;

obstruction, when such occurs, is generally progressive and of slow onset.

Essentially a history of chronic biliary or digestive disturbances or a history of intermittent partial or complete intestinal obstruction in the older age patient presenting symptoms of acute intestinal obstruction, where no weight loss or anemia is noted and no previous abdominal surgery has been performed, should suggest the strong possibility of gallstone ileus. X-ray is diagnostic in a good percentage of cases. Conversely, x-ray is not infallible, as witnessed in the case report by Moloney[12] where a preoperative diagnosis, made essentially by x-ray, of gallstone ileus proved at surgery to be a calcified obstructing fecolith in the appendix. In a number of cases, as with other abdominal pathological states, the final diagnosis will be made only at surgery.

TREATMENT

Treatment is almost always surgical. Wangensteen[6] initially advocated, on occasion, the use of suction and antispasmodics in the hope that the stone would pass spontaneously. In the patient who will not tolerate surgery, this may be indicated as a last resort, but of late years the feeling is that suction should be an adjunctive preoperative or postoperative measure only. Used as a completely therapeutic measure, suction can confuse the diagnosis, mask any subsequent perforation, and lull the patient and physician into a sense of false security.

The second case reported here illustrates this point quite well. General supportive measures such as intravenous fluids, electrolytic replacement, etc., are obviously indicated as required.

Operative excision of the obstructing stone with or without resection as required or indicated should be carried out as soon as the patient can be prepared to tolerate surgery. The initial incision should be over the point of obstruction if such is known, otherwise a right rectus approach can be used and extended as required. "Milking" the stone distally if possible or proximal, if proximal gut dilatation is not excessive, has been considered preferable since a more physiologic bowel wall for repair is secured. Coffey and Willox[4] prefer milking the stone proximally about one foot from the site of obstruction and removing the impacted stone through a small longitudinal incision after isolating the bowel segment with rubber shod clamps. The incision is later closed transversely. Attempts to crush the stone at surgery and trust to later "spontaneous passage" are to be definitely condemned.

Enterostomy proximal to the point of obstruction is rarely indicated now if a Cantor or similar type tube can be successfully passed. Where the obstructing stone is in the large bowel, especially the sigmoid, removal of stones with immediate bowel wall closure or resection with primary anastomosis may be unwise and unsafe. In such cases a proximal or a transverse colostomy, where feasible, can be performed, and operative removal of the stone with or without resection can be carried out at a later date when the patient represents a better surgical risk.

A search for one or more additional stones in the intestinal tract should be made; if more are found, they should be removed to prevent possible subsequent obstruction. The second case serves as an example of this point. X-ray or palpable evidence of gallstones in the gallbladder at surgery is an obvious indication for later cholecystectomy procedure assuming adequate biliary drainage. Essentially then, the main purpose surgically is to relieve obstruction the fastest and safest way possible. Accordingly, cholecystectomy, reparative surgery for present fistulae, etc., are secondary procedures to be done as needed at a later date.

The question of subsequent operative closure of biliary intestinal fistulae is a more difficult problem. As previously noted, Hinchey[3] feels that these fistulae result from obstruction of the common duct and paradoxically may be "life-saving" occurrences. There would seem to be a good deal of truth in this conjecture; in a number of patients operated upon for gallstone ileus, the cholecysto or choledocho-enteric fistulous tracts were noted to have become obliterated by fibrosis following apparent re-establishment of adequate biliary drainage through the usual physiological channels. A physiological approach, when stones are present in the gallbladder, would appear to be a cholecystectomy if adequate drainage of bile is present or can be obtained by surgical anastomosis. (When a choledocho-enteric fistula concurrently or separately exists, the same reasoning would apply plus the additional surgical procedure of closing such a fistulous tract.)

Follow-up cholecystectomy has been proposed as a prophylactic surgical procedure in the older patient with cholelithiasis, with or without a previous history of partial or complete intestinal obstruction by gallstones. This holds for cases where the patient may not be having or have had symptoms from the cholelithiasis.

Concerning cholecysto or choledocho-colonic fistulae, there is a difference of opinion as to further surgery. Wakefield, Vickers, and Walters[1] are of the belief that there is a frequent occurrence of cholangitis and hepatitis, diarrhea, and weight loss in such patients, and accordingly such fistulae should be closed at the earliest possible time. Other authors do not agree. It would seem advisable to close such fistula surgically and do an associated cholecystectomy where cholelithiasis is present, if, as mentioned be-

fore, adequate biliary drainage by the normal channels is present or can be secured by anastomotic surgical procedure.

CASES

The following are the only coded cases of gallstone ileus at the Wesley Hospital, Wichita, from 1920 to January 1, 1952. I wish to express my appreciation to Dr. L. E. Vin Zant and the late Dr. James S. Hibbard of Wichita for permission to present these cases.

Case Number 1: Mrs. C. G., a 62-year-old housewife, entered Wichita Hospital on November 19, 1951, complaining of intermittent colicky abdominal pain of sudden onset for the past four days. Generalized abdominal bloating occurred and was followed by nausea and vomiting of bile stained fluid and undigested food particles. Previous attacks of intermittent abdominal distention and colic, subsequently relieved by bowel action, had been noted off and on since the patient was 40 years old. Severe heartburn, that is substernal and precordial distress, had been noted for the past month.

This patient stated she had experienced indigestion after eating beans, cabbage, onions, and fatty foods. No past history of jaundice or hematemesis was obtained. The patient is a grava V and para V. Emergency scout film of the abdomen on admission showed an area of calcification in the left lower quadrant and small intestinal distention. The patient stated she had had no bowel movement since the onset of her illness and had passed gas only with the aid of enemas.

Past history and systemic review were non-contributory other than as noted.

On the fifth day of hospitalization, she was transferred to Wesley Hospital. Physical examination at that time revealed a well developed, markedly obese, white female in no apparent acute or chronic distress. Temperature was 98.4, pulse 80, and blood pressure 100/70. The patient wore a hearing aid. The sclerae were clear. There was a mild systolic grade I murmur over the aortic area. The abdomen was noted to be markedly obese. Peristalsis was audible. Deep and rebound tenderness was elicited in the right upper quadrant. Laboratory work on admission revealed a complete blood count and urine within normal limits. Serology was negative.

Course in hospital: A diagnosis of gallstone ileus was made. General supportive therapy was immediately started and a Levine tube was passed and connected to continuous suction. The patient was taken to surgery the following morning and a right rectus incision was made. On exploration of the abdomen the terminal ileum was observed to be obstructed by a firm, round, slightly movable mass. The small gut was distended proximally. The obstructing mass was milked distally and the area packed off. The ileum was incised over the mass. A large gallstone measuring 4 x 3 x 3 cm. was removed. The bowel wall was inspected; no areas of necrosis or erosion were seen, and the ileum was closed. The abdomen was

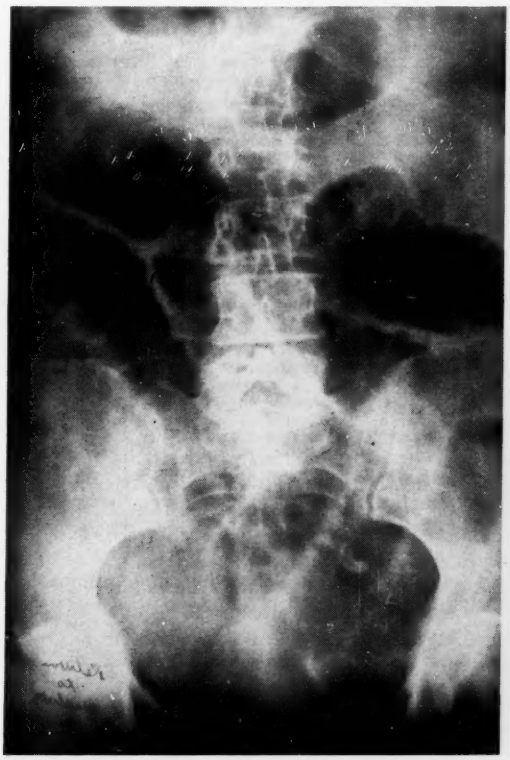

Figure 1. Case 1. Admission scout film of the abdomen showing small intestinal distention with an area of calcification in the left lower quadrant of the abdomen.

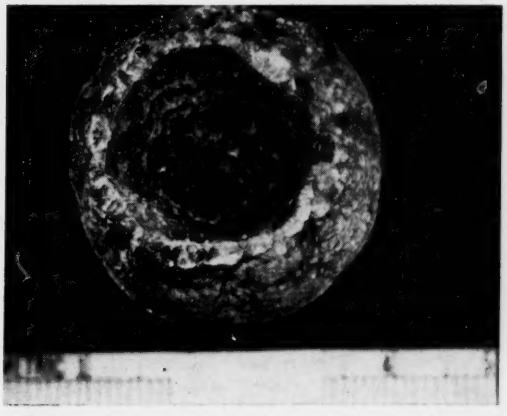

Figure 2. Case 1. The obstructing gallstone removed at surgery measured 4 x 3 x 3 cm.

closed without drainage. The postoperative course was essentially uneventful. Discharge was on the 10th postoperative day.

On January 9, 1952, surgical procedures performed included exploration of the common duct, a cholecystectomy, and closure of a large fistula extending between the gallbladder and the duodenum.

Case Number 2: This case represents two separate admissions and operations and is summarily noted here since it was fully reported previously by Vin Zant and Hibbard.[13]

This 85-year old female presented symptoms of obstruction of four days' duration. X-rays showed a calcified shadow in the right upper quadrant and another calcified shadow in the left midabdominal area at the site of obstruction. A diagnosis of gallstone ileus was made. Conservative therapy because of family wishes was tried for 10 days without success. Surgery was then performed successfully.

About five weeks later the patient presented symptoms of partial intestinal obstruction. X-rays showed an opacity in the left lower quadrant; no opaque shadow was seen in the right upper quadrant although one was so located previously on films five weeks previously. A diagnosis of gallstone ileus was made. Surgery was performed successfully.

SUMMARY

1. The syndrome of gallstone ileus is discussed. Although a relatively rare entity, its usual high mortality is often the result of late or missed diagnosis and delayed adequate surgical treatment. Thus it is an important consideration in the differential diagnosis in an older patient presenting symptoms of acute, partial or complete intestinal obstruction. Clinical features are presented.

2. Treatment of gallstone ileus is essentially and primarily surgical.

3. Follow-up management of patients with reference to any existing cholelithiasis or cholecysto or choledocho-entric or colonic fistulae is still a matter of varying opinion, although subsequent surgical closure of the fistulae or cholecystectomy seems indicated where adequate biliary drainage by natural channels or by anastomotic means is present or can be secured.

4. Two case histories are presented. In each case the diagnosis was made pre-operatively.

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From the beginning of our history, we have been diversified, culturally and racially. It has been a great human experiment which has been launched and conducted on our American shores and plains—perhaps the greatest and most challenging in the history of human society. . . . We have set out here to demonstrate that peoples of all racial strains, of all colors, creeds and cultures, of widely varying background, can be accepted as equals, can learn to live and work and play together and become a firm unity by the force and attraction of noble ideals mutually shared—the dignity and worth of the individual, the equality of all men and the conception of the state as the democratic expression and the servant of free men and women.

—*Ralph J. Bunche*

Hypersplenism Associated with Leukemia

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One of the hematologic complications in patients with leukemia and leukosarcoma which has received increasing attention over the past several years is hypersplenism. The spleen normally exerts control over the number of circulating blood cells by certain inhibitory or destructive mechanisms. Anatomic enlargement of the spleen, whatever the etiology, often results in a physiologic hyperfunction.

Secondary hypersplenism may manifest itself in the form of a hemolytic anemia, produce selective cytopenias such as neutropenia, anemia, thrombocytopenia, or any combination including pancytopenia, which is a reduction in all the cellular elements of the blood, and may be the mechanism in "aleukemic" phases sometimes seen in leukemia. The bone marrow shows hyperplasia for the element deficient in the peripheral blood.

Little is known of the etiologic stimulus except the constant existence of splenomegaly. The exact mechanism is controversial and has been the subject of much investigation.

Doan[13] and his co-workers have for years leaned toward the theory of hypersequestration by the spleen of the deficient blood element or elements, while Dameshek[4] and his associates have championed a humoral hypothesis with the spleen elaborating a substance which inhibits the proper maturation or release from the marrow of the deficient blood elements.

The syndrome which presents the greatest clinical problem and that which has been most extensively investigated is acquired hemolytic anemia related to splenic hyperfunction.

ETIOLOGY AND PATHOGENESIS

In secondary acquired hemolytic anemia, though the immunologic mechanism is obscure, all the classic actions of cell antibodies in vitro have been demonstrated.

Boorman et al.[5] first demonstrated that the immune serum prepared by Coombs, Mourant, and Race[6] by the injection of human serum into rabbits could be used to distinguish certain types of acquired hemolytic jaundice from congenital hemolytic jaundice. They presumed that the agglutination of red cells which occurred was a physical manifestation of the union of the globulin or other substance on the surface of the red cell with the antibody in the test serum. In most cases of immunohemolytic disease the Coombs test is positive, indicating the presence of "coating" antibodies.[25]

In many cases the serum contains free incomplete agglutinins of the warm or cold type,[21] sometimes active in saline but more frequently active in albumin[7] or against trypsin treated red cells.[8] Trypsinizing red cells involves destruction of the surface antigens of the cell with consequent uncovering of deeper structures with antigenic properties. Dodd[9] believes that similarily injured red cells as modified cell antigens may play a large part in hemolytic anemia by initiating auto immunization with production of antibodies with duel specificity for normal and abnormal cells.

A hemolysin is demonstrable in a few cases of acquired hemolytic anemia.[10] Methods have been described by which red cell antibodies can be demonstrated to render cells susceptible to phagocytosis, the opsonic effect.[11]

Administration of small quantities of hemolytic serum in a single injection is sufficient to cause a progressive, fatal hemolytic anemia in the guinea pig with the formation of incomplete auto antibodies, which can be demonstrated in vivo as agglutinins and which possess hemolysing properties.[12]

The actual destruction of these "sensitized" red cells probably takes place in several ways. Intravascular hemolysis is apparently one of the mechanisms, particularly when free auto or isohemolysins are present in the serum. It has been noted in experimental hemolytic anemia in animals that antibodies destroy more red cells in vivo than in vitro.[10] After injection of anti red cell serum into an animal a biphasic reaction occurs. The first phase is one of rapid hemolysis, probably caused directly by amboceptor and complement in the blood. This is followed by a prolonged hemolysis which goes on for several days, generally destroying a larger number of cells and caused by other means, probably a slow mechanical destruction of sensitized cells.[13]

Abnormal red cell antibodies are usually demonstrable as agglutinins. Observations in experimental hemolytic anemia[14] and from direct observation of circulating blood in patients indicates that intravascular agglutination of red cells very probably takes place in immunohemolytic disorders in man. Ag-

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glutinated red cells are more susceptible to trauma, and, according to Castle, Ham, and Shen,[15] the agglutination also brings about hemolysis via erythrostasis with release of injurious substances from autolyzing tissues adjacent to stagnating red cells, blocking small blood vessels.

Hemolysis resulting from the more frequently found "coating" antibodies can best be explained on the basis that the red cells are in some way damaged and thus rendered more susceptible to lysis and phagocytosis. Erythrophagocytosis has been described in acquired hemolytic anemia in the spleen and other tissues.[11] The ability of the splenic macrophages to ingest the sensitized or antibody coated cells but not the normal ones was demonstrated by Brandt et al.[16] Erythrophagocytosis cannot explain the spherocytosis seen in vivo but not in vitro, which may be explained by the sequestering of coated red cells in the spleen and other organs.[17] Neither can the hemoglobinemia frequently found in immunohemolytic disorders be explained by phagocytosis alone.

Although the spleen plays an important part in these syndromes, it is obvious from the results of splenectomy that the role of the spleen varies from case to case. Effects range from complete cure to no change. The antibody titer may decrease rapidly or remain high, even though splenectomy has been of good clinical effect.[18] It seems evident that in at least some cases abnormal antibodies are produced by the spleen.

Wright et al.[7] found higher antibody titers in the splenic blood than in the peripheral blood. Wagley et al.[19] incubated normal red cells with spleen tissue from patients with acquired hemolytic anemia and found the incubated cells to be heavily coated with an agglutinating substance. In other cases, particularly where splenectomy causes clinical improvements but no fall in antibody titer, it would appear that red cells altered by antibodies produced elsewhere are retained in the spleen and destroyed in some manner.[17] Failure of splenectomy may be attributed to the fact that other parts of the reticuloendothelial system may be involved in these processes.[15]

CLINICAL PICTURE AND DIAGNOSIS

In hemolytic disease there is increased destruction of red blood cells in the peripheral blood. Anemia occurs when the rate of destruction exceeds the compensatory capacity of the marrow to replace the cells as they are being destroyed. Normally when the red cell has reached the end of its life span it is broken down in the reticuloendothelial system, and particularly the spleen, into a hemoglobin and a pigment portion. The iron and protein portions of hemoglobin are retained within the body while the pigment portion is freed into the blood stream as the normal serum bilirubin. The bilirubin passes via the liver into the gastrointestinal tract where it is reduced and excreted as fecal urobilinogen. A portion of the latter is reabsorbed into the blood stream and re-excreted via the kidney as the normal urinary urobilinogen.

In hemolytic anemia more red cells are destroyed, resulting in a greater liberation of bile pigment into the blood stream, an elevated serum bilirubin, and possibly a jaundiced patient. More pigment is excreted via the liver into the gastrointestinal tract, the excretion resulting in an increased fecal urobilinogen, and concomitantly more of this is reabsorbed into the blood stream to be excreted via the kidneys as an increased urinary urobilinogen.

With excessive hemolysis, therefore, we find evidence of increased hyperplasia involving the erythropoietic elements in the bone marrow, liberation of red blood cells into the peripheral blood with reticulocyte counts as high as 50 per cent, and breakdown of the normal marrow barriers so that younger nucleated red cells may appear in the peripheral blood.

On the other hand, we expect to find evidences of increased blood destruction with elevated indirect plasma bilirubin, increased fecal and urinary urobilinogen, spherocytosis with increased fragility of the red cell, and anemia. The serum bilirubin may be normal, but fecal urobilinogen is always elevated.

An important characteristic of hemolytic anemia is the rapid destruction of transfused red cells in the patient's circulation. Loutit and Mollison,[20] employing the Ashby technique, noted that normal red cells became Coombs' positive and disappeared in 10 to 40 days from the recipient's circulation in contrast to a normal life span of 120 days, which has been substantiated by studying cells tagged with radioactive chromate.[22] The need for large amounts of blood to maintain hemoglobin and red cell count without obvious blood loss points to a hemolytic process.

In acquired hemolytic anemia the most common immunologic finding is a positive antihuman globulin (Coombs') test, though it may be negative[39] and has on occasion been found positive in certain congenital hemolytic syndromes.[7] The indirect Coombs' reaction may be positive when other methods have failed. The serum of these patients usually contains a panagglutinin capable of reacting with cells of their own blood group or normal human group 0 cells, which can be demonstrated by testing in several media at various temperatures.

Erythrocytes treated with trypsin or papain[8] may be used to detect abnormal antibodies. Failure to detect antibodies may be due in some cases to the presence of large amounts of cold precipitable cryoglobulin.[23] Another manifestation of a heightened

capacity to form antibodies is the frequent occurence of biologically false positive tests for syphilis. Heterophile antibody is sometimes produced.[24]

A factor of some diagnostic and therapeutic import is the difficulty often encountered in correctly typing the patient's blood. Because of the marked tendency to auto agglutination, the patient may be incorrectly typed as AB Rh positive. If any suspicion exists, the red cells should be thoroughly washed with saline and typed at 37°C.[32]

THERAPY

1. Transfusions: In hemolytic anemia the effect of transfusion is short and the added difficulty of precipitating hemolytic crises is introduced, which will result in a lower rather than increased red count.[40] In many cases even frequent transfusions are inadequate. Transfusions are primarily useful when given in conjunction with steroid therapy or splenectomy.

2. ACTH and Cortisone: Since these syndromes are apparently due to adverse antibody reaction, the trial of corticotropin and cortisone, known to exert a beneficial effect on diseases of hypersensitive causation, was rational. Dameshek[34] and Gardner[35] were the first to report favorable results in treatment of acquired hemolytic anemia with ACTH. These hormones may decrease the severity of blood destruction, with a rise in hemoglobin, erythrocyte count, and hematocrit and a decrease in serum bilirubin and fecal urobilinogen levels. A positive Coombs' test may or may not become negative.[24] More often there is a marked drop in titer of hemolysins and iso-agglutinins.[24, 37] In some instances the disease is arrested or can be kept under control for months.[39] However, in most cases, remissions can be maintained only with continued therapy.[43, 44]

Dameshek postulated that ACTH may alter the milieu of the red cell, to suppress antibody production or adsorption of hemolytic proteins on the cell surface and thus prevent hemolysis. However, with hemolytic anemia caused with phenylhydrazine, there is no question of immune bodies or adsorption of proteins; yet ACTH and cortisone significantly alleviate anemia caused by this chemical in adrenalectomized rats.[36] Bethel et al.[41] suggest that they modify splenic dysfunction. Gardner[35] found a decrease of mechanical and osmotic red cell fragility in some instances after administration of ACTH. Garcia[38] believes that ACTH primarily increases production and delivery of red cells to peripheral blood.

Cortisone seems to be as effective as ACTH.[39] Most patients treated with transfusions when needed and cortisone, 100 to 200 mg. daily, show some improvement in 7 to 14 days,[32] but the degree and length of response is unpredictable, and continued steroid therapy is usually necessary to maintain results.[42] Smaller doses may be effective for maintenance. A restricted intake of sodium, the addition of potassium salts, and the administration of testosterone to offset negative nitrogen balance must be considered in long term steroid therapy.

3. Splenectomy: Splenectomy in leukemia and leukosarcoma has been reevaluated in the past 10 to 15 years. Until 1940 results were poor and mortality rate high, since it was frequently performed empirically as treatment of the fundamental malignant process which is unaltered by splenectomy. Bryant (1866) was the first to report removing the spleen for leukemia. Billroth (1866) and Kocher (1888) were the first to perform splenectomy for leukosarcoma of the spleen. Mayo, reporting 60 cases of splenectomy in leukemia and leukosarcoma (1928), considered splenectomy to be palliative and indicated in young patients.

A more rational approach was initiated by Ferrata and Fieschi[47] in 1939, recognizing the clinical and hematologic manifestations of hypersplenism as the indication for splenectomy. Since 1940 many reports of small series of cases have been published, indicating that the operation is of value when performed for relief of a co-existing hypersplenism.[26, 33, 39, 40] Good results have been obtained in the majority of cases where presence of hemolytic anemia and hypersplenism, thrombocytopenia or pancytopenia was the criterion. Only in cases in which great discomfort results from an extremely large spleen is splenomegaly without hypersplenism an indication for splenectomy.

The largest series of cases was reported by Fischer, Welch, and Dameshek[33] in March 1952. Splenectomy was performed on 18 patients with leukemia and leukosarcoma, using these criteria. In 8 patients the hemolytic anemia or cytopenic disturbance was controlled from 1 to 5 years. Three received benefit for 3 months. Three patients received no benefit.

For best results, the bone marrow should be hyperplastic, and the finding of a markedly diminished number of megakaryocytes or nucleated red cells in the bone marrow represents a contraindication to splenectomy.[33, 46]

Splenic puncture may be helpful in some cases to rule out extra-medullary hematopoiesis. A trial with ACTH or cortisone before splenectomy is indicated.[44]

Results of splenectomy are not predictable, but in the majority of cases remissions are produced with a mortality rate from operation only slightly higher than that for splenectomy in more favorable situations, in spite of the serious condition of many of these patients. Since management is difficult and prognosis poor in many cases without splenectomy, the operation is definitely a useful measure and probably should be done more frequently in selected cases.

CASE NO. 1

UNIVERSITY OF KANSAS MEDICAL CENTER

An 80-year-old housewife was first seen on December 27, 1953. She complained of progressive weakness and easy fatigability for 2 months following intestinal flu. General health had been good except for bronchial asthma of 30 to 40 years' duration. She had had no attacks during the preceding two or three years. Two years before admission she had an attack of arthritis involving knees and ankles, completely relieved with cortisone. She had bruised easily all of her life. Various hematinics had been tried without improvement. Her skin was pale, and there were numerous ecchymoses on both hands and forearms. There was no lymphadenopathy. Sclerae were slightly icteric, and fundi showed grade 3 arteriosclerotic changes. The heart was somewhat enlarged, and there was a grade 2 aortic systolic murmur and a grade 3 apical harsh systolic murmur. Abdomen was obese, and the tip of the spleen could be palpated far laterally.

Laboratory work on admission gave the following results. Urine showed a trace of albumen. Blood chemistry and electrolytes were within normal limits, as were findings on the kidney, ureter, and bladder examination. Electrocardiograms showed left axis deviation. A chest x-ray revealed an enlarged heart with suggestive evidence of substernal thyroid. Sedimentation rate was 45 in 35 minutes. Gastric analysis was normal. A hemogram showed a red cell count of 1,680,000 with marked anisocytosis and macrocytosis, an occasional spherocyte, and 1 nucleated red cell per 100 white blood count. Hemoglobin was 5.9 grams or 37 per cent, hematocrit 46 per cent, reticulocytes 48.4 per cent with 242,000 platelets, white blood count 27,150 with 77 per cent lymphocytes, 22 per cent polymorphonuclear leucocytes, and 1 per cent monocytes. Indirect serum bilirubin was 2.6 mg. per cent, direct 0.4 mg. per cent. Urinary urobilinogen was 2.6 mg., fecal urobilinogen 348 mg. Prothrombin time was 75 per cent of normal. Red cell fragility test was slightly increased. Direct Coombs' reaction was 4 plus.

Bone marrow study showed erythroid hyperplasia and lymphocytic infiltration with cells of chronic lymphatic leukemia. Megakaryocytes were observed scattered throughout.

A diagnosis of chronic lymphatic leukemia and hemolytic anemia was made.

The patient was given three blood transfusions and then was started on cortisone, 100 mg. daily. Six days later, following two more transfusions, her red count was 3,550,000 with hemoglobin 11.8 grams (76 per cent), reticulocytes 21.4 per cent. The Coombs' test remained 4 plus, serum bilirubin decreased to 1.4 indirect and 0.2 mg. direct, urinary urobilinogen fell to 0.7 mg., and hemoglobin was sustained at 11.8 grams at the end of the one week. However, fecal urobilinogen was 728 mg.

This patient was obviously icteric, with increased serum bilirubin and red cells hemolyzing at a terrific rate, as indicated by the elevated reticulocyte count, and high urinary and fecal urobilinogen, yet she managed to maintain her count fairly well, presumably due to intensive compensatory hyperplasia. Though the reticulocyte count, serum and urinary urobilinogen steadily decreased, fecal urobilinogen remained elevated and the Coombs' test continued strongly positive in spite of cortisone therapy. She was discharged on 100 mg. of cortisone daily.

Cortisone was decreased to 75 mg. per day on February 15, 1954, and on February 22 she was given 3.5 mc. of P_{32} orally. She continued to feel well, but the Coombs' test remained 4 plus, reticulocyte count ranged from 18 to 35 per cent, and hemoglobin gradually dropped to 9.3 grams (60 per cent) with a red count of 2,650,000.

She was admitted to the hospital on April 1, 1954, for transfusions and evaluation. Reticulocyte count was 22.8 per cent, nonprotein nitrogen 45, serum bilirubin indirect 1.5, fecal urobilinogen 453 mg., and urinary urobilinogen 5.7 mg. Because of her advanced age and arteriosclerotic heart disease with calcific-aortic stenosis, constituting a surgical risk, the advisability of splenectomy was debated. It was concluded that the hemolytic process could be controlled for some time with cortisone and transfusions. A blood transfusion of 1,000 cc. was given, and cortisone was increased to 100 mg. daily.

On April 12, 1954, her hemoglobin was 10.8 grams (70 per cent), red count 3,140,000, reticulocytes 16.6 per cent, Coombs' test 4 plus. It was felt that splenectomy was not indicated in view of the relative contraindications to surgery and fairly good response to treatment.

CASE NO. 2

VA HOSPITAL, KANSAS CITY, MISSOURI

A 58-year-old man was first found to have chronic lymphatic leukemia in February of 1947. He complained of weakness and fatigue of one year's duration. His leukemia was adequately controlled and normal red count was maintained with intermittent courses of x-ray until August of 1952, when his red count began to drop. On November 14, 1952, his red count was 1,720,000, hemoglobin 5.5 grams (34 per cent), hematocrit 19 per cent, platelets 112,000, white blood count 18,300 with 62 per cent lymphocytes, 1 per cent monocytes, and 1 per cent eosinophiles.

He had become increasingly weak. Physical examination showed generalized lymphadenopathy. There was an occasional rale in the right lung base. The liver was palpable one finger below the right costal margin. The spleen extended 4 or 5 fingers below the left costal margin and was not tender. A right direct inguinal hernia and bilateral hydrocele were present.

Urinalysis showed 10 to 12 white blood cells per high power field. Bleeding time, clotting time, and red cell fragility were normal. Serum bilirubin indirect was 1.5 mg., direct, 0. Quantitative serology was 4 Kahn units with a negative complement fixation. X-rays of the chest showed infiltration of the right apex and an elongated tortuous aorta with calcifications in the knob. Bone marrow studies showed hyperplasia of the erythroid series with mild lymphocytic infiltration.

On December 5, 1952, after seven transfusions, red count was 3,050,000, hemoglobin 10 grams. He was discharged on hematinics.

The patient was readmitted on December 24, 1952, because of increasing anemia, weakness, and anorexia. Physical findings were essentially the same as before except that the spleen at this time was below the umbilicus and there was 2 plus pedal edema.

Laboratory studies showed a red count of 2,400,000, hemoglobin 7.5 grams, hematocrit 23 per cent, white blood count 7,800 with lymphocytes 56 per cent, indirect bilirubin 1.9 mg. per cent. Secondary hypersplenism with hemolytic anemia was suspected although the Coombs' test was negative.

He was started on cortisone, 50 mg. every 6 hours, and was given 14 transfusions over 36 days. Red count rose to 5,260,000, hemoglobin 14.5 grams, white blood count 27,800 with 77 per cent lymphocytes. Appetite and strength improved. Cortisone dosage was gradually decreased to 25 mg. daily with maintenance of red count. He was discharged January 31, 1953.

He was again admitted on March 7, 1953, with an upper respiratory infection and temperature of 102 degrees. In addition to the previous physical findings, there was a pale icteric tint to the sclerae and the skin.

Red count on admission was 1,320,000, hemoglobin 4 grams, platelets 74,000, white blood count 15,000 with 76 per cent lymphocytes. Serum bilirubin was elevated to 3.1 mg. per cent, all indirect. Urinary urobilinogen was 3 Ehrlich units, and prothrombin time was 45 per cent of normal. Bone marrow showed a definite increase in lymphocytic infiltration but an adequate number of erythroid and myeloid elements. Six transfusions were given.

The febrile illness responded to antibiotics. On March 14, with the red count 3,800,000, hemoglobin 9.6 grams (62 per cent), cortisone dosage was increased to 200 mg. daily. Cortisone was slowly reduced to 100 mg. daily by April 3, with sustained red cell counts at 4,000,000, hemoglobin 10.6 grams. One transfusion was given on April 17, with increase in red count to 4,350,000, hemoglobin 10.8 grams. Cortisone dosage was reduced to 50 mg. daily with a slow steady drop in red cells to 3,200,000 by May 19. On June 1, red count was 2,100,000, in spite of the fact that 3,500 cc. of blood had been given over this period. Cortisone dosage was then increased to 200 mg. daily (June 6), reduced to 150 mg. daily on June 14, and to 100 mg. daily on June 25. A total of 5,000 cc. of blood was given from June 3 to June 28 with no remission in the hemolytic process.

Since control of the hemolytic anemia with cortisone and transfusions was a staggering problem, splenectomy was planned in the hope that some reduction in the number of transfusions and amount of cortisone required by the patient would be effected.

On July 13 red cell count was 3,530,000, hemoglobin 10.0 grams, hematocrit 33 per cent, platelets 92,000, and reticulocytes 15 per cent. Splenectomy was done on July 15 with removal of a 1,500-gram spleen and two small accessory spleens. At the time of operation 1,000 cc. of blood was given.

Improvement was rapid and spectacular after splenectomy. Red cell count had increased to 4,590,000 by July 20, hemoglobin was 13.8 grams (90 per cent), hematocrit 44 per cent, platelets 180,000, reticulocytes 2.9 per cent. Cortisone was discontinued. The patient was discharged on August 12 with marked clinical and hematologic improvement. He was seen again on November 3, at which time the red cell count was 3,920,000, hemoglobin 12 grams (72 per cent), platelets 190,000, white blood count 14,200 with 81 per cent lymphocytes, and reticulocytes 0.7 per cent. A hematinic was prescribed. The patient's count continued to drop, and on December 29 it was 2,030,000, hemoglobin 8 grams (48 per cent), reticulocytes 5.6 per cent, and fecal urobilinogen 115 mg. At that time 1,000 cc. of blood was given.

On January 28, 1954, his hemoglobin was 6.4 grams (38 per cent), serum bilirubin indirect 4.5 mg. Cortisone, 75 mg. per day, was started, and some improvement in the blood picture was noted by February 19. However, his hemolytic anemia seemed to be recurring. Cortisone was increased to 100 mg. per day, and 500 cc. of blood was given. On March 22 hemoglobin was 14 grams and Coombs' test was positive for the first time.

He felt well until April 4, when he was admitted with pain in the right chest, temperature of 103 degrees, and x-ray signs of pneumonia involving the

right upper lobe. He was treated with antibiotics. Surprisingly enough, his hemoglobin, which was 11.1 grams on admission, increased to 13.6 grams by April 20, with a red count of 4,500,000. At that time his lungs were clear, he was afebrile, and he was feeling fine.

This patient presents a difficult problem in management. His hemolytic anemia appeared 5 years after the diagnosis of chronic lymphatic leukemia. He rapidly reached the point where the number of transfusions required to maintain his red cell count was prohibitive, and only continued administration of extremely large doses of cortisone was at all effective. Splenectomy gave him at least a nine months' remission, and the possibility of continued control appears encouraging.

SUMMARY

Patients with leukemia and leukosarcoma may at any time during the disease process develop a syndrome of hemolytic anemia or cytopenia related to the splenomegaly accompanying these clinical states as a secondary or symptomatic hypersplenism.

Incomplete auto antibodies of many types have been demonstrated in patients with acquired hemolytic anemia. Actual destruction of antibody sensitized red cells has been found to be by intravascular hemolysis, intravascular agglutination, with mechanical trauma and lytic action on the vulnerable red cell clumps, sensitization by antibody with subsequent sequestration and hemolysis or phagocytosis in spleen and other organs.

Clinical findings in secondary hemolytic anemia, in addition to those of the primary disease, are indications of increased red cell production and simultaneous excessive destruction. There is a rapid breakdown of transfused red cells. The direct or indirect Coombs' test, and reaction with trypsin treated red cells or normal Group O red cells under certain conditions may demonstrate iso-antibodies.

Transfusions are useful in most cases, but transfusion alone is of limited value. ACTH and cortisone have been used with favorable results, but response is uncertain and unsustained in most cases, and continued steroid therapy is usually necessary to maintain remission. Since 1940, good results have been reported in the majority of cases following splenectomy, when hypersplenism is the criterion for operation. Bone marrow hyperplasia is a prerequisite, and a trial with ACTH or cortisone before splenectomy is indicated.

Two cases are presented to illustrate problems encountered in this hematologic complication of leukemia and leukosarcoma.

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Arrhenoblastoma

G. E. Kassebaum, M.D.

El Dorado, Kansas

Arrhenoblastoma of the ovary presents one of the dramas of medicine, and its apparent rarity leads us to report two cases which occurred in our relatively small hospital within a period of 10 years. G. Barzilai[1] reported 50 cases on record up to 1949. C. Y. Thomas et al.[2] reported 121 cases up to 1951.

There has been much confusion in the nomenclature of this tumor, i.e. adenoma tubulare carcinomatosum, fibroblastic sarcoma of ovotestis, carcinoma, and endothelioma. The most generally accepted name now is arrhenoblastoma, so designated by R. Meyer, who first identified the varied patterns of this tumor as belonging to a special oncologic group.

Histogenesis of arrhenoblastoma is still unsettled. R. Meyer's theory, probably the most accepted, suggests that the early development of the ovary is identical with the testis. In the later stages of female differentiation, certain elements of male differentiating potency may be left in the medullary portion of the ovary. Another theory is that arrhenoblastoma always arises in an ovotestis and is based on actual observation of one case (Barzilai). Others feel that the tumor arises from remnants of the rete testis.

Arrhenoblastomata occur in very young as well as in old patients, perhaps most commonly in the 20- to 30-year group. Our younger was 14 years of age and the older 56. Meyer reported one at 60 years.

The tumor is usually unilateral. It may retain the shape of the ovary or be rounded, lobular, or smooth. The outer surface is bluish or yellowish in color. The size varies from that of a pea to a large grapefruit, and the tumor may entirely replace the ovarian tissue. Mostly solid, the tumor may contain small cysts filled with serous or bloody fluid. Small tumors are usually hard and the larger ones soft, due to necrosis and hemorrhage. On cut surface the tumor shows mottled areas of bluish-purplish-yellowish hues. The tumor does not adhere readily to adjacent structures. Coincident atrophy of the uterus and opposite ovary is usually present. Extension to other parts of genital organs or peritoneum is rare, except in some malignant cases.

The microscopic picture is usually polymorphocellular. The following cellular structure may appear in varied combinations:

1. Spindle shaped or rounded cells resembling early undifferentiated cell type of the early mesenchymal core of the gonads.
2. Large spherical cells resembling granulosa cells.
3. Cuboid or low columnar cells resembling Sertoli's cells of the male gonad. Neither sperm cells nor any of their progenitors have been found.

Arrhenoblastoma is a hormonally active tumor. This is proved by the marked signs of virilization which regress after its removal and reappear if the tumor recurs. Symptoms due to its hormonal activity give the tumor its distinctive position among ovarian neoplasms.

The first changes to appear are always those of de-feminization: cessation of menses, sterility, and flattening and atrophy of breasts. Later follow the masculinizing signs. The figure loses its normal female curves and assumes the more angular male conformation. Masculine hair distribution develops over the body and on the face. In progressive cases, a true beard and baldness have been known to occur.

* El Dorado Clinic, El Dorado, Kansas.

Acne is frequently present. The expression of the face becomes masculine. The voice becomes deep and coarse. The ligaments and cartilages of the larynx appear enlarged. The clitoris hypertrophies but the sexual impulse remains feminine.

Almost all signs and symptoms disappear after the removal of the tumor and usually do so in the order of appearance. Changes in the larynx and clitoris are usually irreversible.

Arrhenoblastoma is classified as a malignant tumor but is far less so than other epithelial tumors. Simple surgical removal usually effects a cure. If, however, symptoms do not regress following surgical extirpation of the tumor, metastasis has probably occurred and the outlook is grave. Irradiation should be carried out in all cases where pathologic study suggests marked malignancy.

CASE REPORTS

Mrs. K. H., 56, nullipara, was admitted July 1, 1942, complaining of a bearing down sensation in the pelvis and perineum. Her menstrual life had been regular and had ceased eight years before. She reported, however, that four months earlier she had menstruated for several days, an occurrence which was repeated twice later. Hirsutism of face and abdomen was markedly increased, and some huskiness of the voice was noted.

The pathological report following dilatation and curettage indicated low grade carcinoma of the fundus. She was given x-ray therapy on July 2, 1942, followed by a total hysterectomy, including tubes and ovaries. The left ovary, the size of an apple, was found to be hard and nodular; the right ovary was atrophied; the fundus was small with multiple calcified nodules; the cervix was normal. The pathological report was arrhenoblastoma, left ovary.

Miss B. B., 14, nullipara, was admitted February 13, 1952. Although she may have been a little early in maturing, she showed normal physical development. Menses, beginning at 11 years, had been normal until six months previously, when amenorrhea began, with light spotting at times. Three months before admission the patient suffered an acute sore throat, and hoarseness had been persistent since that time.

Physical examination disclosed an abdominal tumor which was gradually enlarging and an increased growth of hair on her upper lip. An ear, nose, and throat examination showed bridging of cords as found in chronic laryngitis.

A laparotomy was performed February 14, 1952. A multilocular, semi-solid and cystic tumor about the size of a grapefruit was filling the lower abdominal cavity. The pedicle of the tumor was crushed and cut. The remainder of the right tubo-ovarian ligament and the right fallopian tube were excised. The left tube and ovary were normal and were left intact.

Following is the pathological report:

Macroscopic examination: The specimen consists of a 6- or 7-inch cystic mass of ovarian tissue presenting many multiloculate cavities, some areas of gelatinoid yellowish tissue. There is also a 5 x 60 mm. appendix.

Microscopic examination: Diffuse fibrosis is revealed throughout the ovary with irregular cord-like masses of cells which have a pinkish cytoplasm of moderate amount. The nuclei vary in size and in staining characteristics, generally are ovoid, moderately dark staining. At times the cytoplasm is box-like in character. In areas, these cells are forming an irregular lacy mesh work with a number of glandlike spaces lined by cubical epithelial cells of moderate height. There are some areas of fibrosis, and, in some instances, the cells grow in cord-like masses. They appear to be malignant but well within the confines of the tissue. In view of the type of growth, the grade of malignancy remains questionable. These tumors appear malignant but behave in a benign manner. This, however, may be considered as a malignant growth, at least from the microscopic appearance. The capsule of the ovary appears to be relatively intact, but the growth characteristics are otherwise those of a malignant process. The diagnosis is arrhenoblastoma, a malignant neoplasm.

Four months later the menses returned. Gradually the hirsutism disappeared, but two years after operation the voice remains hoarse, which is usually true in these situations. The patient remains in good health and apparently there are no metastases.

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I know of no safe depository of the ultimate powers of society but the people themselves, and if we think them not enlightened enough to exercise their control with a wholesome discretion, the remedy is not to take it from them, but to inform their discretion by education.—*Thomas Jefferson.*

THE MONTH IN WASHINGTON

Editor's Note. The following summary of Washington news was prepared by the Washington office of the A.M.A. for distribution to state and regional medical journals.

With the change in control of Congress, there naturally will be a major reshuffling of all committees, including those handling medical and health legislation. A new chairman moves to the top, and at the bottom a few Republican members drop off, to be replaced by an equal number of Democrats. In a Congress so evenly divided, domination of this committee machinery is a vital asset.

A majority of the Democrats taking over committee chairmanships in January will be returning to the same jobs they held when their party was in power, but the situation is a little different on the two committees most important in health and medical legislation. It will be the first time either of these chairmen has had the responsibility of running the full committee, although both have been involved in medical legislation for many years. Both are veteran legislators and are Southerners. They are Senator Lister Hill of Alabama, who replaces Senator H. Alexander Smith of New Jersey as chairman of the Labor and Welfare Committee, and Rep. Percy Priest of Tennessee, who succeeds Chairman Charles Wolverton, also of New Jersey, on the Interstate and Foreign Commerce Committee.

By reason of seniority, Senator James Murray of Montana is in line for the Labor and Welfare Committee chairmanship. However, he has announced that he prefers to run the Interior and Insular Affairs Committee, thus turning over the other chairmanship to Senator Hill. Senator Murray, as a sponsor of national compulsory health insurance, and as a chairman and member of its committee that held such turbulent hearings on this subject, became well known to the medical profession.

Senator Hill, the son of a physician, has been in Congress for 30 years—14 in the House before he came to the Senate. He was a co-sponsor of the Hill-Burton hospital construction program, perhaps the most important piece of medical legislation enacted since World War II.

Presumably the Senate committee's Health Subcommittee again will be headed by Senator Herbert Lehman of New York, who handled this task during the last Democratic Congress, the 82nd.

Mr. Priest is a former school teacher and newspaperman. He has been in the House for seven uninterrupted terms. In 1951 he was chairman of the Commerce Committee's Health Subcommittee; the subcommittee system was abolished by the committee in 1952. Since then he has taken an extremely active part in committee work in health and medical fields.

The Hill and Priest committees will handle most health legislation with the exception of military, veteran, and appropriation bills. For example, they will be in charge of reinsurance if it is reintroduced, as well as most health-medical bills originating in the Department of Health, Education and Welfare.

A number of other committee changes of importance to medical legislation are scheduled. Rep. Edith Nourse Rogers of Massachusetts, a veteran of 29 years in the House, loses the chairmanship of the Veterans Affairs Committee. She is being succeeded by Rep. Olin Teague of Texas, who was elected to Congress for the first time while he was completing his six-year Army duty in 1946.

The House Appropriations Committee chairmanship goes from Rep. John Taber of New York to Rep. Clarence Cannon of Missouri; both have the reputation of being economy-minded. Of considerable significance in medical appropriations is the change in the chairmanship of the subcommittee that handles money for the Department of Health, Education and Welfare. The chairman for the last two years, Rep. Fred Busbey of Illinois, carefully scrutinized all health appropriations and effected many reductions. He was defeated for re-election. The prospective chairman of the subcommittee, Rep. John Fogarty of Rhode Island, repeatedly has intervened in the committee and on the House floor to restore money cut out by the subcommittee.

Chairman of the Armed Forces Committee in the Senate—where medical care for military dependents would be taken up—will be Senator Richard B. Russell of Georgia, replacing Senator Leverett Saltonstall of Massachusetts. On the House side, the Armed Forces chairmanship goes to the veteran Rep. Carl Vinson, also of Georgia. He replaces Rep. Dewey Short of Missouri.

Any bills proposing reorganization of the executive departments will come before Chairman John L. McClellan of Arkansas in the Senate and Rep. William L. Dawson of Illinois in the House. They are succeeding Senator Joseph R. McCarthy of Wisconsin of Rep. Clare B. Hoffman of Michigan.

(This summary is, of course, predicated on the Democrats surviving a threatened recount of the close Senate vote in Oregon and going ahead with organization of both chambers.)

Plan now to attend the 96th annual session of The Kansas Medical Society, Hutchinson, May 1-5, 1955.

PRESIDENT'S PAGE

Within a few days we will have entered 1955 when problems relating to the physical well being and the health of people will again be spread before our legislative chambers.

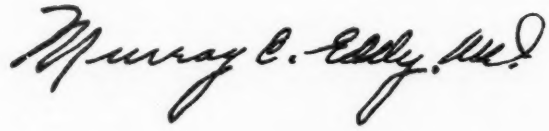
At the federal level, Congress will deliberate a reinsurance program and a hundred other items that will in one way or another influence the health of the American people. Kansas will once more determine the minimum education requirements for physicians.

We have collectively elected persons to speak for us on these and other issues. We will now be governed by their wisdom. If we hold a conviction upon an issue and have experience to support our belief, we are morally obligated to express our view. As citizens, we owe elected officials the benefit of our special knowledge in the field of health.

In this coming fateful and decisive year, it is my earnest hope that you will each fulfill your very special role in giving the public the highest possible quality of health care. This implies not only your professional services as a physician but your duty as a citizen.

Therefore, the New Year's resolution for myself will be just that, and with the heartiest and most cordial greetings on this occasion for you and for your family, permit me to add the sobering reflection that we must each participate in this coming venture if we shall continue to give the public the benefit of sound and progressive health legislation.

Yours,



EDITORIAL COMMENT

New Year's Resolutions

Next year will be different. My New Year's resolutions are already made to give me a running start before the scoring begins. There will be just five which for some unaccountable reason all begin with the letter c, perhaps because they go into effect on Christmas eve. Here they are.

I will be curious. During the year I shall prepare two scientific papers, one for oral presentation and the other for publication. This is not vanity on my part but a deliberate effort to organize my thinking upon two separate subjects, to perform a mental exercise for the benefit I personally will receive thereby.

I will be critical. For the coming year I intend to be increasingly critical of organized medicine at all its levels. I plan to discover what medical organization means and how it functions. I shall not one year longer be led unknowing and unwilling into paths I cannot see. So, speaking for one member, I intend to learn what my society hopes to accomplish and shall then exert an honest effort to either change its course or serve its purpose. So I will be critical and zealous in my effort because I alone am personally involved in what succeeds or fails.

I will be considerate. Here my confidence begins to waver because I find myself at the threshold of an indefinable area. Perhaps the subject is ethics. It certainly relates to professional conduct. Of course, we all intend to render the best possible professional care, but I have something else in view. I want to be considerate of my patient, not only as a patient but as an individual who in his mind is the most important living person. If that means trouble, at least it is my own. And I have elected to assume its consequences.

I will be a citizen. I will analyze my obligations to my country, state, and to the town in which I live. Once this reflection has been completed, I propose to abandon my present lethargy and undertake not less than one project, unrelated to my profession, which I may actively pursue with honesty and with enthusiasm to completion.

There is one more, another c. I know, it was the earnest resolution for this one year at least to wish you each a Merry Christmas before the holiday has passed. So I shall do so now and, whatever happens to the other four, one resolution will have been carried to reality, and even on that basis alone the next year will be different.

Federal Aid in Kansas

Part III

This portion of the story of federal aid in Kansas will briefly discuss several areas, again without critical comment. The series is intended to provide the physician with factual information rather than to discuss purposes or values.

EDUCATION

Federal aid for educational purposes is among the larger sums obtained in Kansas. There are five programs in this field, three of which are administered by the superintendent of public instruction and the last two are operated by the Vocational Education Department.

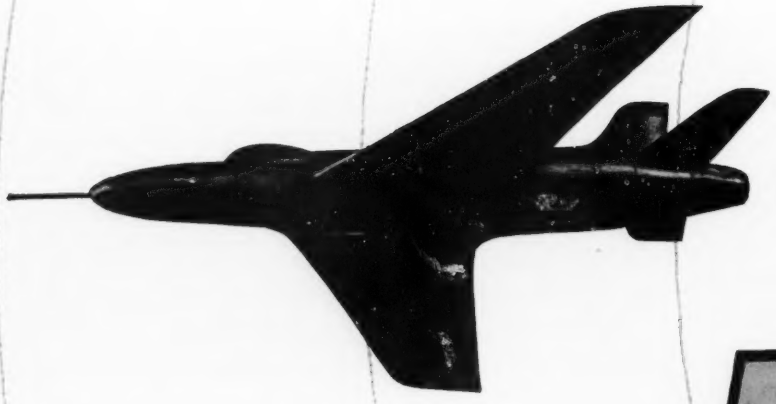
The national school lunch program was authorized by Congress in 1946. It is federally administered by the U. S. Department of Agriculture. The Superintendent of Public Instruction directs the program for the state and the Board of Education locally. The formula is involved, taking into account the school census, the per capita income as compared with the national figure, etc. Federal aid has been relatively constant over the years and in 1953 was $788,900. The state paid $26,585 and local sources contributed $3,341,132 for a total of $4,156,617. In Kansas, 1,086 schools participated in this program.

The next two items are emergency grants, first for school construction and second for maintenance and operation of schools in areas upon which the federal government has placed financial burdens by reason of civilian or armed forces activities. This is a little involved because of the variety of coverage, so an analysis will not be attempted here except to say that the federal government gave Kansas $2,600,000 for this purpose in 1953 and Kansas paid $10,000.

VOCATIONAL WORK

There are two programs for which Vocational Education last year received $366,810.26 from federal sources, $250,000.37 from the state, and $789,108.94 locally for a combined cost of $1,405,919.57. This is about constant over the years except that the federal grant is decreasing slightly and local participation expanding. The money is used for instruction, teacher training, etc. A sizable portion of the cost goes for veterans' training. There have been 11,156 veterans enrolled in this program.

Vocational rehabilitation in Kansas has received federal aid since 1937. This is all operated by federal and state funds with no local participation. The formula is simple. The federal government pays the entire cost of administration, the entire cost of vocational guidance and placement services for each state, and half the cost, as long as there are funds, for rehabilitation training, tools and equipment, books,



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living expenses during rehabilitation, medical treatment, hospitalization, and prosthetic devices. The program is open to physically or mentally handicapped persons over 16 years of age and is designed to render them fit for remunerative employment. Last year Kansas spent $276,718.59 for this program, of which $184,866.50 was federal money and $91,852.09 state.

HIGHWAYS

The Federal Aid Road Act was passed by Congress in 1916. Kansas has participated in this program since 1917. It is federally administered by the U. S. Department of Commerce, at the state level by the Highway Department, and locally by the county commissioners. Grants are based on population, land area, and post road mileage of the state compared with United States totals and are generally on a 50-50 basis. Figures are available for all types of roads, but the total only is given here. In 1953 the federal government gave Kansas $12,573,566 for roads. The state spent $10,247,558, and local sources spent $3,119,686 for a total of $25,940,810. So federal aid in this category is about half the expenditure and, considering federal grants to all states totalling $575,000,000, Kansas received 2.1 per cent.

LABOR

The only item listed pertains to unemployment compensation and employment service. Federal participation is limited to administrative costs of the state agencies. The fund is originally raised by a three per cent tax on all payrolls with eight or more employees. Actually this program has changed recently, but the 1952 report is the latest available. Three tenths of one per cent of this tax is forwarded to the general treasury of the United States, so Kansas keeps 2.7 per cent for local allotments. The federal government pays all administrative costs of the offices conducting these services which, for Kansas at least, have never equalled the amount sent in. In 1952 Kansas paid the federal government $2,325,000, representing three tenths of one per cent of the three per cent tax. The government financed a state and 26 local employment offices at a cost of $1,435,200, which represents a net loss for that year of $889,800.

The fourth in this series, to appear next month, will deal with the welfare program.

A Message From the Auxiliary

Yuletide greetings to you from the Woman's Auxiliary to The Kansas Medical Society!

The co-operation, understanding, and helpfulness of your president, Dr. Murray C. Eddy, have been a wonderful Christmas gift to us lasting the year through. We are also most grateful to the Advisory Committee of The Kansas Medical Society for the approval of our goals and programs and for the many inspiring and constructive suggestions to us.

I wish to take this opportunity to express some thoughts on our mutual problems.

The magazine *Today's Health* concerns all of us. The complimentary six months' subscription sent to your office will soon expire. Won't you send in your subscription fee of $1.50 to Mrs. Chester Young, 4315 Victory Drive, Kansas City, Kansas. Through "Operation M.D." it is possible to have *Today's Health* in the waiting room of every doctor in the United States. If this magazine could be self-supporting by an increase in circulation and advertising, the deficit made up each year by the A.M.A. would be available for other needed programs.

The membership of the Auxiliary has been foremost in my thoughts. The Kansas Medical Society and our group form a partnership. Every doctor should be proud to have his wife as a member. Enroll her so she may assist the Auxiliary in its program for the advancement of medicine, public health, and public relations. State and national dues are $2.00. Send your check to Mrs. Louis Graves, St. John, Kansas.

Civil defense is one of our problems. All of us agree that America will need more effective civil defense if we are going to brace this country for the shock of a possible attack with modern weapons and survive that attack with enough people and productive facilities to go on and win a war. Doctors have adopted the philosophy of mutual aid and reciprocal assistance. Encourage your wife to work with her Auxiliary so she may aid the medical profession in meeting responsibilities and in spreading its philosophy to everyone. The reading of Philip Wiley's book *Tomorrow* should jar any person from the spirit of complacency.

Our Auxiliary believes that a deterioration of our medical training standards would be a national disaster. We are giving our wholehearted support to the American Medical Education Foundation. Each of our 2,000 members has been asked to contribute $1.00 to this foundation.

Doctors realize more than we the need for more nurses. To help recruit girls for this vocation, we have established an extensive loan program. Additional encouragement is given by local auxiliaries and hospitals. Twenty-six counties are actively engaged in nurse recruitment programs. Fifteen Future Nurse Clubs have been formed with auxiliaries serving as sponsors. Their membership is approximately 500 girls.

May we remind you of our Auxiliary Memorial Fund for nurse scholarships. If anyone wishes to give a memorial in the name of a deceased Auxiliary member or friend, money may be sent to Mrs. Rich-

ard O'Donnell, Ellsworth, Kansas. She in turn will send a card to the family of the deceased.

Lately I have deliberated on the resolution "A Doctor for Every Doctor's Family." The need of a personal physician for the doctor and his family should be heeded. The medical profession has a higher death rate than that of any other profession in our country. It is exigent that doctors regard with care the advice given them by their family physician. Doctors must live longer; they are needed. A strong healthy doctor is a wonderful advertisement to the medical profession.

All that our Auxiliary does is done to aid the medical profession. At any time, call on us to help you. Never underestimate the power of your Auxiliary.

At this holiday season may the spirit of Christmas be in your heart and bring you joy all the year through.

—Elizabeth Millis, President
Woman's Auxiliary to The Kansas Medical Society

P.S. As a reminder—more people die in traffic on December 24 than on any other day of the year. "Don't give your life for Christmas."

Age and Distribution of Doctors

A recent study of the age and distribution of Kansas physicians has revealed a number of interesting facts. This survey includes reports on 1,816 physicians in Kansas.

Effects of the Kansas Plan, originated in 1948, may be realized by a study of the over-all picture. In 1948 the average age of the doctor in Kansas was 54.6. Today, or after five years, the average is 49.8 as a result of the influx of younger doctors in Kansas. The median age likewise dropped proportionately, and today that age is 46. The oldest member of the Society is 98 years of age and the youngest is 25. There are 364 members of the Society under 36 years of age.

Information on doctor distribution in 1948 is not available. The records today show 79 physicians practicing in 68 Kansas towns with populations under 500. One hundred twenty-two are located in 87 communities with populations ranging between 500 and 1,000, making a total of 201 practicing in towns having fewer than 1,000 residents. Cities having populations of from 1,000 to 5,000 persons receive services from 480 physicians. Ten communities in Kansas have populations numbering between 5,000 and 10,000, and 146 physicians have chosen to locate in those cities. The remaining physicians in the survey, 989, practice in cities of more than 10,000 residents.

The Executive Office of The Kansas Medical Society maintains a locations list for the aid of communities in need of physicians and physicians seeking locations.

BLUE SHIELD

The presence of participating physicians at most of the district Member Council meetings this fall was enthusiastically received by the members.

All members of Kansas Blue Cross-Blue Shield are privileged to participate in activities of the plans by expressing their opinions and wishes through the organization known as Blue Cross-Blue Shield Member Council. District council meetings are held twice each year.

Member Council is a representative group of members who speak independently of the plan. It is organized on the county, district, and state level; it is the "voice of the members," which trustees and staff listen to and consider seriously in planning the best possible benefits for Kansas people.

One-third of the Blue Cross Board of Trustees is composed of lay members. Each of the nine Member Council districts elects a member to the board. The remainder are elected by the state Members Committee. The chairman of the state Members Committee is also one of three lay members on the Blue Shield board.

The active participation by Blue Shield doctors in these meetings has done much to stimulate interest and create understanding between the member and the medical profession. The objective discussion of community health problems takes on new meaning to the member when a doctor lends professional opinion to the meeting. At the same time, public opinion is accumulated by the profession.

Success of these meetings suggests that, at some future date, it might be desirable to hold district meetings involving all groups of the Blue Cross-Blue Shield program, the doctors, the hospitals, and the members. Through this type meeting a mutual understanding of health needs and solutions could, perhaps, best be attained.

Medical Education Expands

Medical education has expanded considerably since 1945, according to a recent study made by representatives of the Association of American Medical Colleges. During the period covered, three medical schools have opened, the University of Washington, the University of California at Los Angeles, and Miami. Two, Alabama and North Carolina, have expanded to a four-year curriculum.

Biopsy Procedures in Office Practice

Tumor Conference

Edited by Irwin Joffe, M.D.

Dr. Helwig: Biopsy as a diagnostic technic was introduced by the German pathologist, Ruge,[1] in the 1800's. Between that time and the start of the present century, it fell into disrepute largely due to the inadequate training of pathologists, who often misinterpreted what they found in the tissues examined. For the last 50 years, however, biopsy has been a standard procedure. We should recall that no cancer, except under rare circumstances, should be treated before a positive diagnosis by biopsy has been established. The literature and the experience of all of us are replete with instances in which the patient has been mistreated because a biopsy was lacking or was wrongly interpreted.

I can't emphasize too strongly that when you send a specimen to your favorite pathologist you accompany it with every bit of pertinent data available. This would include the sex, age, and race of the individual, the duration, location, and gross character of the lesion, and history of previous biopsy or treatment. The pathologist's morphologic interpretation must frequently be guided and modified by clinical information, which allows him to study tissues in the perspective of their relationship to the general status of the patient. You are doing your patient no service, and you are doing yourself no service, and you are doing the pathologist distinct disservice if you don't give him every bit of data which you have at hand.

I'm going to ask Dr. Robinson to tell us about some of the pitfalls to avoid in the taking of biopsies.

Dr. Robinson: In general, when dealing with a large, accessible neoplasm, one should excise with the cold knife a small piece of the viable margin of the tumor along with a little of the adjacent normal tissue. A small tumor may often be managed best by excision biopsy of the entire lesion. Perhaps some of the greatest difficulties are encountered in the deep biopsy. The physician who attempts such a biopsy through a small incision is likely to come up with something less than the tumor. Such a biopsy gives no information and may give a false sense of security.

Another common pitfall in taking a biopsy is to take the most obvious part of the tumor, the most exposed part. The sample selected may be completely necrotic, or may be composed entirely of exudate. The pathologist can't reach a diagnosis with material of this character.

Proper biopsy of lymph nodes requires care and judgment. Nodes in the region of ulcerated or recently treated lesions may enlarge as the result of inflammatory changes alone. Usually, but certainly not invariably, such inflamed nodes are less than 1 cm. in diameter. Larger lymph nodes in the drainage area of a neoplasm must be viewed with more suspicion since they will frequently contain metastatic tumor. Select the right node. Don't take a tiny node that's off to the side simply because it is easy to get; it may not give any useful information. Take a large node that's in the obvious lymphatic drainage area of the primary tumor, or one which seems obviously involved by lymphoma. Usually the entire node should be removed with capsule intact.

Beware of taking lymph node biopsies through small incisions. I'll never forget one of the first cervical nodes that I was asked to remove as a junior resident. I was working through a little nick over the front of the neck when suddenly the floodgates opened and I couldn't see or feel anything. A man of experience, the senior resident, literally bailed me out rather quickly and simply by tying off the jugular vein, which I had inadvertently opened. Always secure adequate exposure if you are going to invade an area where you can get into trouble.

Dr. Helwig: Thank you, Dr. Robinson. Dr. Proud, will you tell us something about biopsies in the hidden cavities of the head and neck.

Dr. Proud: In taking biopsies from the nose and throat, one will require an effective local anesthetic; the most effective one in my hands has been cocaine, a 5 per cent solution. One can probably avoid trouble by preparing the patient in the following manner. Perform the biopsy shortly after the patient has eaten. The incidence of hypoglycemic syncope and cocaine reaction is greater before meals. A preanesthetic dose of a barbiturate 15 minutes before the application of cocaine solution is also advisable. Use a vasoconstrictor drug locally. It will help to fix the cocaine to the tissue and give better analgesia. It will also diminish systemic absorption of cocaine. Use cocaine sparingly and accurately; wring out the applicators before applying the drug. Repeated applications of small amounts are more effective than one

Cancer teaching activities at the University of Kansas Medical Center are aided by grants from the National Cancer Institute, U. S. Public Health Service, and the Kansas Division of the American Cancer Society. Dr. Joffe is a Trainee of the National Cancer Institute.

copious application because the cilia carry much of it away.

I think the hardest area to approach for an adequate biopsy is the nasopharynx. The laryngologist often uses a palate retractor as an aid to visualizing this area. The general practitioner, however, does not need a $20 palate retractor for biopsying the nasopharynx. A couple of rubber catheters will do just as well. One of them is passed into each nostril and out of the mouth; each catheter is then held taut by clamping its two ends with a hemostat. Then, with the use of the tongue blade and the mirror, one can examine the nasopharynx satisfactorily; and, having someone hold the tongue down, one can slip a conchotome through the nose and under indirect visualization with the mirror one can see the nasopharynx and watch the biting forceps snip off a specimen of tumor. Obviously some of the rules that Dr. Robinson has laid down for us will not be strictly followed in taking biopsies from the nasopharynx. It is hard enough to get a biopsy, and it is often impossible to select accurately areas where tumor tissue is invading the normal. I'm afraid our biopsies—those of the nasopharynx particularly—are probably some of the worst that the pathologist receives.

In the nasopharynx there is one type of tumor that should never be biopsied; it is the tumor known as the nasopharyngeal fibroma.[2] This tumor is extremely vascular, and even when unmolested it has been known to bleed fatally. Every now and then some physician applies an adenotome to one with the intent of performing an adenoidectomy and becomes so fascinated in bailing out the blood that the patient exsanguinates before the physician realizes what has happened. A nasopharyngeal fibroma is smooth, an adenoid is rugose. A nasopharyngeal fibroma is purplish-red, an adenoid is pale. A nasopharyngeal fibroma is hard, whereas an adenoid is compressible. It is wise to visualize and palpate the nasopharynx before attempting a biopsy.

To take a biopsy from the nose, a nasal speculum and a conchotome are necessary; the nasal speculum will expose the nasal fossa, and the biopsy can be taken with the conchotome. Now there are two types of conchotomes or forceps. One is a cup forceps, and I know the pathologists resent it because it crushes the specimen. The other type, the punch forceps, has sharp edges and punches out a piece of tissue which is considerably less distorted.

A pack should always be available when biopsying in the nose. Brisk bleeding is occasionally provoked, and if a pack is handy it may eliminate considerable anguish. The best type of pack for controlling immediate hemorrhage is a small cotton pledget soaked in epinephrine, which is inserted promptly after the biopsy is taken. The resultant vasoconstriction will help to prevent hemorrhage. If a bulkier pack is needed over a longer period, it should be coated with petrolatum.

When physicians take tissue from other parts of the body, they send it to the pathologist to find out what it is, but it has become popular to discard structures removed from the nose or the ear; all too often they turn out to be malignant. Tissue that comes out of the ear, the nose, or the throat should be studied by the pathologist, just as other tissues.

To biopsy in the ear with any satisfaction, one has to have a very small biopsy forceps. Obviously, the size of the specimen which one will procure with such a forceps is not going to thrill the pathologist. The biopsy can be accomplished through an ordinary ear speculum or through the electric otoscope. Upon finding exuberant granular tissue in the middle ear, one is tempted simply to cauterize it to make it go away. Believe me, tumor can occur in the ear, just as it can occur anywhere else in the body; and when granular tissue is found in the ear, it definitely should be biopsied. Before manipulating a growth in the ear, one should exclude the presence of the glomus jugulare tumor,[3] a vascular neoplasm which sometimes extends into the aural cavities. This tumor is purplish-red and usually produces pulsating tinnitus which the patient likens to the sound of a locomotive; he hears a swish with each heartbeat. Such a sound can also be heard by the examiner

Figure 1. Distorted tissue of uterine cervix in biopsy secured with cautery knife (mag. x100).

upon auscultation. If gentle manipulation with a probe initiates brisk bleeding, a biopsy should not be attempted.

Biopsies of the larynx and hypopharynx are best left to the specialist. A good biopsy of the tongue must be a deep one, and a deep one quite often will lead to hemorrhage. Lesions of the gingiva in people with dentures may be due only to irritation by the dentures; if they are of recent onset, biopsy may be deferred during a trial period of 2 to 3 weeks without dentures.

Dr. Helwig: Thank you, Dr. Proud. I'd like to add one other tumor which sometimes bleeds profusely, and that's the hemangioma.

Dr. Boley, may we have your comments?

Dr. Boley: I have selected a few slides to illustrate some of the points made by Dr. Proud and Dr. Robinson. As was pointed out, the choice of instruments is most important in determining the quality of the material that reaches the pathologist and consequently influences the character of his interpretation. Select a delicate forceps to avoid crushing tissue and, above all, avoid the cutting cautery.

I would like to show a miscroscopic slide of tissue (Figure 1) that was removed from the cervix with a cautery knife. As we scan the section, we note that the heat of the cautery has distorted or destroyed every cell in the fragment. No interpretation is possible; the efforts of the referring physician and the inconvenience and expense to the patient have been in vain. If the cautery is used to achieve hemostasis, it should be applied only after the biopsy has been secured with the use of the cold knife.

If a biopsy is to be satisfactory, the quantity of tissue must be adequate. The next section I have selected to show (Figure 2) is an example of an inadequate uterine curettage. One sees desquamated cells from the vagina and small amounts of blood. The few microscopic fragments of endometrium seen are inadequate for interpretation. You must submit adequate material if you want a diagnosis.

Another item which deserves emphasis is proper fixation of biopsy material. Prompt fixation in an adequate amount of 10 per cent formalin or other fixative will prevent distortion due to drying. Lymphoid tissue is particularly vulnerable to drying and to rough handling and should be given special care.

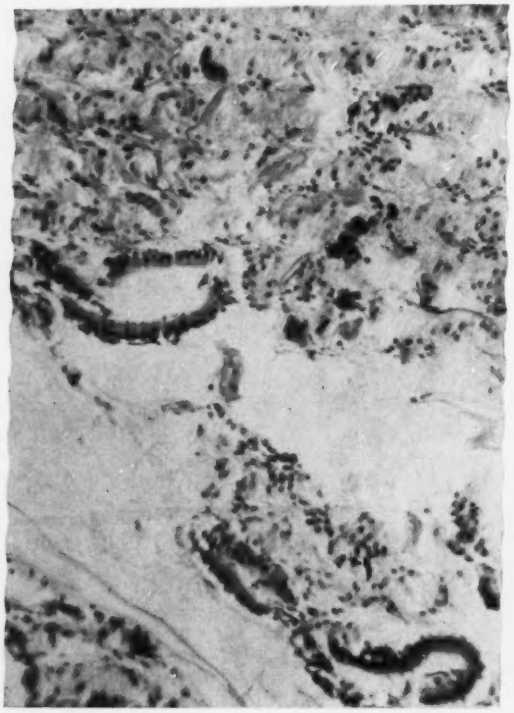

Figure 2. Inadequate uterine curettage showing a few fragmented endometrial glands and cellular debris (mag. x100).

Figure 3a. Biopsy of vulval skin which was allowed to dry prior to fixation (mag. x100).

Figure 3b. Properly handled biopsy from adjacent site showing carcinoma in situ (mag. x100).

Better preservation of lymph nodes will be achieved if they are halved before being placed in fixative. In fact, half of the node may be reserved unfixed for bacteriologic cultures, a technic too often neglected. Not uncommonly, microscopic study of a lymph node discloses only a non-specific inflammatory process. Definitive diagnosis and accurately directed treatment may depend on the results of bacteriological investigations.

The next specimen (Figure 3a) was allowed to dry. There is no way that the pathologist can redeem a piece of tissue that has been mishandled in this way. Interestingly enough, a re-biopsy of this patient's vulval lesion, properly handled, disclosed carcinoma *in situ* (Figure 3b). It is the physician's responsibility to see that tissues are properly handled.

I'd like to show you one example of a proper biopsy taken from the rectum (Figure 4). Several fragments of tissue were received and processed. In one of these fragments, beneath intact mucosa and deep to the muscularis mucosae, are several little nests of tumor cells. This specimen enabled the pathologist to reach a diagnosis that might easily have been missed had the biopsy been less complete. This was a recurrent carcinoma that didn't show ulceration on the surface.

The last specimen that I would like to demonstrate was supplied by Dr. R. E. Johnson and deals with the aspiration biopsy. The patient from whom this tissue was removed gave a history of removal of a

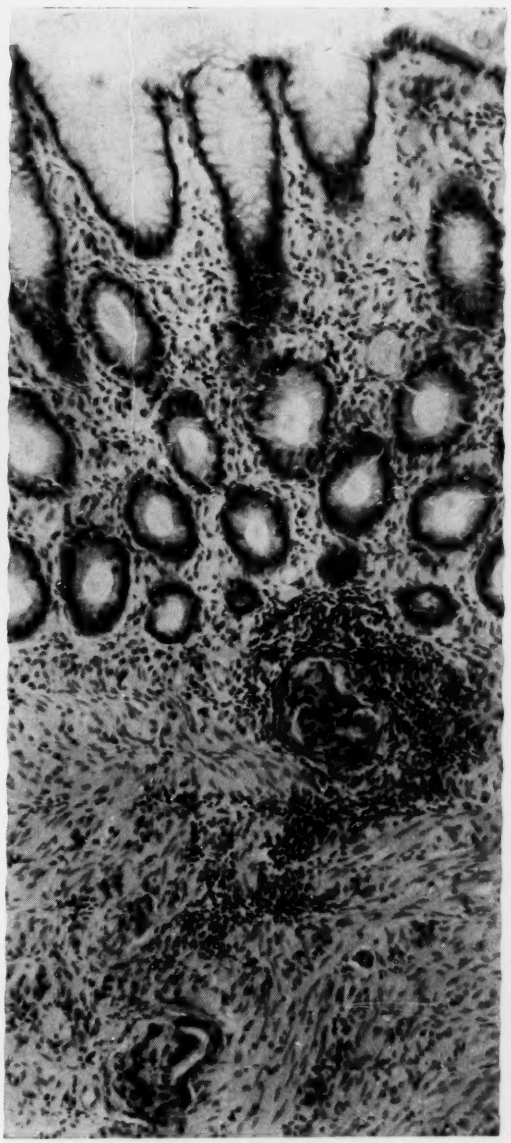

Figure 4. Rectal biopsy showing deeply situated nests of tumor cells beneath intact mucosa (mag. x100).

mole from the temporal area one year earlier. The mole had been treated with cautery, and no tissue was examined by a pathologist. A recurrent, rapidly enlarging nodule developed in the preauricular area on that side. Aspiration biopsy of this mass disclosed melanoma. Radical resection of the area followed a few days later, and a microscopic section shows extensive seeding of tumor cells along the biopsy needle tract (Figure 5). One cannot needle malignant tumors with impunity. If aspiration biopsy is done on a tumor that proves to be malignant, the entire needle tract must subsequently be removed, as was done in this case.

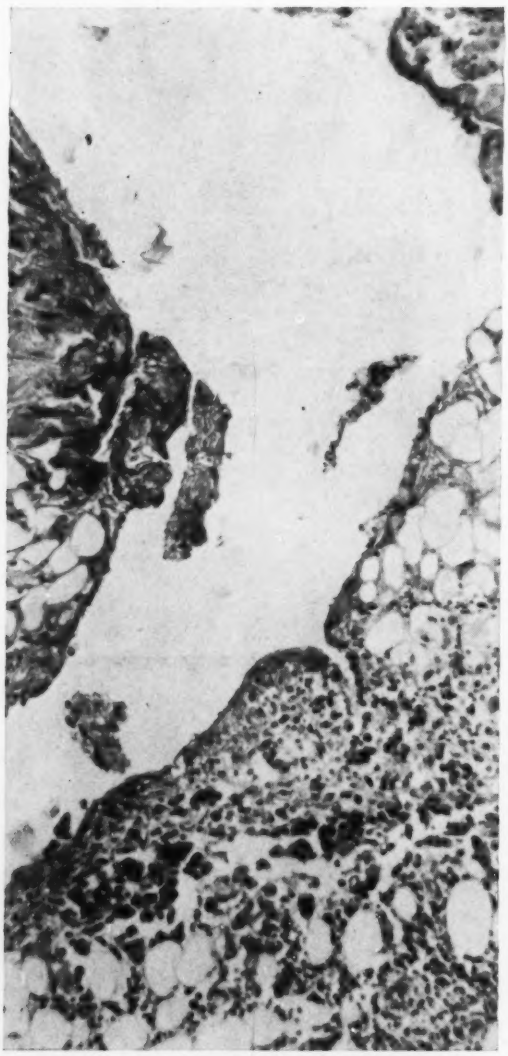

Figure 5. Depths of needle tract showing melanoma cells disseminated in subcutaneous fat (mag. x100).

Dr. Helwig: Dr. Johnson, do you care to comment?

Dr. Johnson: If aspiration biopsy is contemplated, the anticipated information should be of specific importance to the individual patient concerned. Otherwise, he should not be subjected to the risk of implantation of tumor by means of that aspiration. Secondly, we attempt to minimize the risk in operable cases by placing the needle tract in such a position that the subsequent surgical procedure can remove it.

The reason we aspirated a melanoma—some people would argue that one should never tamper with a melanoma in that way—was this. About one month before this 40-year-old man came to us, he developed a small nodule in the preauricular area on the right. The examination showed some little spots of pigment around the periphery of a flat achromic scar in the temporal region and a 3 cm. nodule in the preauricular area. We were suspicious, of course, that we were dealing with a melanoma, but because the situation called for wide excision of the skin of the face, total parotidectomy, and a radical neck dissection, including loss of the facial nerve, we felt that we should have histologic proof that it was melanoma and not some relatively benign lesion. So we did the aspiration biopsy, putting the needle tract in a position so that it was included in the subsequent radical dissection in continuity.

Dr. Helwig: Thank you, Dr. Johnson. I would like to add a note to what Dr. Robinson said about total excision biopsy. By removing for biopsy entire small skin lesions of less than 2 cm. in diameter, the physician will, in many instances, cure the patient. I would also like to emphasize the limited accuracy of the clinical diagnosis of certain types of skin lesions; xanthomas, seborrheic keratoses, histiocytomas, papillary pigmented basal cell epitheliomas, and others are often difficult to distinguish clinically. One dermatologist of wide experience has told me that his clinical impressions of this type of lesion are wrong in 20 per cent of instances. The average observer can't hope to do as well, and since these lesions can be eradicated by biopsy, this would appear to be the proper way to manage them.

Dr. Pollak, would you like to say a few words about the cervical smear?

Dr. Pollak: Cytologic diagnosis is a valuable technic in an office practice, provided the smears are taken properly. It is my personal opinion that a cervical smear should be a part of the routine pelvic examination. The making of the cytologic smear should be done by the physician; it should not be delegated to a technician. The smear should be made at the beginning of the examination, before lubricants have been introduced. Furthermore, the patient should

not have douched or bathed just before the specimen is acquired. I much prefer cervical smears to vaginal smears since I find that they yield more information.

Dr. Helwig: I would add that any mucus found in the cervical canal should be made a part of the smear; it often contains trapped cells. Always fix smears immediately, before they dry, in equal parts of alcohol and ether. Slides should remain in the fixative for 30 to 60 minutes and can be stored in this solution for weeks. A clean slide coated with glycerin will serve to cover the smear for mailing. Mailed slides should be carefully protected; the usual slide container too often proves inadequate.

Dr. Tice: One point that hasn't been mentioned is the medicolegal aspect of the biopsy. In treating cancer, radiologists often have to push treatment to the point where rather extensive damage occurs in tissues adjacent to the tumor. It is always a degree of satisfaction to have the pathologist's diagnosis of cancer as a basis for extensive therapy.

Dr. Robinson: I would like to make just one more point clear. As clinicians, we work with the pathologist in the interest of the patient. We are not antagonists of the pathologist. In the course of our examination of the patient we are likely to form a definite clinical impression concerning the patient's disease. When the pathologist doesn't confirm our impression we should get together with him and talk it over, and perhaps in conference we can arrive at a proper conclusion. Repeated biopsies are sometimes necessary to reach the correct diagnosis. One shouldn't relinquish clinical impressions too easily. The pathologist is removed from the patient; he often doesn't see the entire picture. Therefore, when he returns a negative report or one that is contrary to a strong clinical opinion, a discussion of the matter should follow. In a fair proportion of cases the diagnosis of the clinician will ultimately be confirmed.

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Statistics show that in 1927 the average cost of a case of lobar pneumonia was $1,000 and included the loss of at least five or six weeks of work. The chance for survival was only 3 to 1. In 1953, an average case of lobar pneumonia involved the loss of less than two weeks and was treated with antibiotics that cost from $15 to $30. The chance of survival was 25 to 1.—*Graydon L. Walker, Parke, Davis and Company.*

MID-WEST CANCER CONFERENCE

The seventh annual Mid-West Cancer Conference, sponsored by the Kansas Division of the American Cancer Society and the Committee on Control of Cancer of The Kansas Medical Society, will be held at the Broadview Hotel, Wichita, on Thursday and Friday, March 24 and 25, 1955.

Committees planning the event have been working for months to arrange a program of interest to every physician in the state. Guest speakers who are widely known in the various specialties of medicine will take part in the session. There will be one big social event, a banquet for physicians and their wives, on Thursday evening.

Dr. Robert Dulaney Moreton, associated with the Tom B. Bond Radiological Group, Fort Worth, will be one of the speakers. Dr. Moreton is clinical assistant professor of radiology at the University of Texas, Southwestern Medical School. He is a fellow of the American College of Radiology and is a member of the Radiological Society of North America, Roentgen Ray Society, and Rocky Mountain Radiological Society. In 1949 he received two awards, one of which was a gold medal from the American Medical Association for an exhibit he had prepared and the other from the Association of Military Surgeons.

Also taking part in the program will be Dr. C. C. Little of Bar Harbor, Maine, who received his Sc.D. degree from Harvard University in 1914. Dr. Little has been active in cancer work for many years and in 1950 was winner of the American Cancer Society award for "Distinguished Service to Cancer Control." He is the author of a book, *Civilization Against Cancer,* published in 1939 and is a fellow of the National Academy of Sciences, New York Academy of Medicine, and National Institute of Social Sciences.

Biographical material about the other speakers will be published in subsequent issues of the JOURNAL. Names of the speakers are as follows: Dr. Richard Chamberlin, Philadelphia, radiologist; Dr. Elson B. Helwig, Washington, D.C., pathologist; Dr. John R. McDonald, Rochester, Minnesota, pathologist; Dr. J. Herbert Nagler, Philadelphia, oncologist; Dr. George T. Pack, New York, surgeon, and Dr. Henry K. Ransom, Ann Arbor, Michigan, surgeon.

COUNTY SOCIETIES

The new offices of the Sedgwick County Medical Society, 1102 South Hillside Avenue, Wichita, were formally opened on Sunday, October 24.

A scientific meeting of the society was held on November 2. Speaker was Dr. S. Gilbert Blount, Jr., assistant professor of medicine, University of Colorado Medical Center, Denver, who spoke on "Pathophysiology and Treatment of Chronic Cor Pulmonale."

Members of the medical societies in the first district entertained their wives at a dinner meeting held at the Sabetha Country Club on October 26. Dr. Frederick E. Wrightman, Sabetha, councilor for the district, presided. Speakers were Dr. Murray C. Eddy, Hays, president of The Kansas Medical Society, and Mrs. E. R. Millis, Kansas City, president of the Auxiliary.

A joint meeting of the Crawford County Medical Society and its auxiliary was held at the Hotel Besse, Pittsburg, November 4. Mr. Carl Brown and Mr. Lee Haworth were speakers, outlining local plans for civil defense and the part assigned to members of the medical profession.

Dr. Mahlon H. Delp, chairman of the Department of Postgraduate Education at the University of Kansas School of Medicine, was speaker at a meeting held at the Marion City Building on November 4. Present were physicians from Marion, Harvey, and McPherson counties.

About 50 persons were present at a meeting at the Concordia Country Club on November 4 when the Cloud County Medical Society entertained a number of guests. At the program following a dinner, Dr. Murray C. Eddy of Hays and Dr. John L. Lattimore and Mr. Oliver E. Ebel of Topeka were speakers.

Dr. Veryl J. Elson and Dr. Jack G. Rowlett, Paola, discussed "Virus Infections" at the October meeting of the Miami County Society held at the Presbyterian Church in Paola.

A meeting of the Wyandotte County Society was held at the City-County Health Building, Kansas City, on November 16. Dr. Richard F. Schneider discussed "Psychiatric Problems in General Practice," and Mr. John B. Smith, superintendent of the Winfield State Training School, told of the facilities available at the school and the work it is accomplishing.

Dr. Don C. Campbell, of the Mayo Clinic, was guest speaker at the November 1 meeting of the Shawnee County Society at Topeka. His subject was "Some Problems Related to the Anemias."

The Osage County Medical Society met at the Hotel Coffee Shop, Osage City, on October 22. Wives of the members were guests at a dinner which preceded the program. Speakers were Dr. Don C. Wakeman and Dr. John E. Crary, Topeka, who discussed "Diabetic Acidosis and Coma."

Dr. Philip W. Morgan, Emporia, was guest speaker at a meeting of the Cowley County Society held on October 21.

Members of the Harvey County Society and their wives met on November 4 at the Hotel Ripley, Newton. Dr. George Westfall, Jr., Halstead, was speaker of the evening.

Dr. Thomas A. Weldon, Perry, was host to the Jefferson County Society at a meeting held on October 28. A film on mental disease was shown.

Dr. Robert A. Dobratz, Chetopa, was elected president of the Labette County Society for 1955 at a meeting held at the Parsons Country Club on November 10. Dr. Arthur P. Burgess, Oswego, was named vice-president, and Dr. I. J. Waxse, Oswego, became secretary.

Diabetes detection drives were sponsored by three county societies, Atchison, Lyon, and Pratt, during "Diabetes Week," November 14-20. In Atchison County, free tablets for testing were provided through local drug stores. In Lyon and Pratt counties, physicians examined specimens from grade school students and from adults who asked for the service.

A meeting of the Wilson County Society was held in Neodesha on November 10, and the following officers for 1955 were elected: president, Dr. John W. McGuire, Neodesha; vice-president, Dr. Hugh G.

Bayles, Fredonia, and secretary-treasurer, Dr. Charles E. Stevenson, Neodesha.

The Committee on Public Relations of the Wyandotte County Society, under the chairmanship of Dr. Tony Dillon, is participating in a program of the American Cancer Society. Volunteers are being trained to visit the homes of persons chronically ill with cancer. Four physicians, Dr. Galen M. Tice, Dr. P. E. Hiebert, Dr. C. C. Nesselrode, and Dr. Maurice Laing, were instructors at the first session on "The Physical Problems of the Cancer Patient."

ACTIVITIES OF MEMBERS

Dr. George L. Thorpe, Wichita, attended the 105th annual session of the Indiana State Medical Association in Indianapolis late in October. He participated in a panel on "Emergencies" on October 26 and spoke on "Modern Office Therapeutics" before the general practice section of the meeting on October 27.

Among the speakers at the Sixth Annual Kansas Conference on Family Life held at Wichita on October 23 were Dr. Warren F. Bernstorf, Winfield, and Dr. Franklin D. Murphy, Lawrence.

Dr. S. Albert Scimeca, who has been practicing in Wichita, has announced the opening of an office in St. John.

Dr. Henry Laurens, Jr., Salina, recently completed a short postgraduate course at Temple University School of Medicine, Philadelphia, on the subject of diagnosis and treatment of diseases of the esophagus.

Dr. Howard V. Bair, superintendent of the Parsons State Training School, attended the Mental Hospital Institute of the American Psychiatric Association at Minneapolis, Minnesota, recently. He was certified by the group as a competent mental hospital administrator and was the recipient of one of the Achievement Awards for 1954.

The life story of Dr. William G. Norman, Cherryvale, was published as a feature story in the October 31 issue of the *Independence Reporter*. Dr. Norman, who is 82 years of age, has been in practice for 56 years, 47 in Cherryvale.

The Sedgwick County Medical Society announces that three of its members have returned to civilian practice after serving in the armed forces, Dr. Earnest P. Carreau, Dr. Perry D. Petterson, and Dr. William C. Swisher. All practice in Wichita.

Dr. Charles C. Hawke, Winfield, was speaker at the October meeting of the Cowley County Medical Assistants' Society held at the Snyder Clinic, Winfield.

Dr. Robert L. Stevens and Dr. Mildred J. Stevens, Garnett, returned last month from a trip to Europe. They were among 600 physicians from 52 countries attending the Eighth General Assembly of the World Medical Association, held in Rome. Other highlights of their trip were attending receptions given by the mayor of Rome and the mayor of Naples and participating in a group audience with Pope Pius XII.

Dr. Junior D. Burger, who has been practicing in Nickerson for six years, has announced plans to move to Hutchinson around the first of the year to practice there.

Dr. Joseph C. Shaw, Topeka, is the author of a column on early transportation which was published as a "Horse and Buggy Days" feature in the *Topeka Daily Capital* on October 25.

Dr. Daniel S. Roccaforte, who has completed two years as a surgeon with the Air Force at Smoky Hill Air Force Base, Salina, was recently released from service. He has returned to his practice at Hanover. Dr. Jack A. Haley, who practiced in Hanover during Dr. Roccaforte's absence, will leave soon to begin a residency in surgery.

Dr. Wayne L. Fowler, Concordia, recently attended a course in "Current Concepts in Internal Medicine," offered by the Chicago Medical Society.

The American College of Surgeons, at its annual meeting in Atlantic City last month, inducted 1,100 new fellows. Kansans in the group are Dr. Don R. Abbuehl, Chanute; Dr. Ernest C. Brandsted, McPherson; Dr. Stanley R. Friesen and Dr. Creighton A. Hardin, Kansas City; Dr. James E. Hill, Arkansas City; Dr. Alfred H. Hinshaw and Dr. Jerome S. Menaker, Wichita; Dr. Gaylord E. Manahan, Lawrence, and Dr. James A. McClure, Topeka.

DEATH NOTICES

Benjamin Smith Morris, M.D.

Dr. B. S. Morris, 54, an active member of the Central Kansas Medical Society, died at a hospital in Kansas City on October 24. Although he had been in poor health for several years, he had continued to practice in Quinter until three weeks before his death.

Dr. Morris, a graduate of the University of Kansas School of Medicine in 1925, practiced first in Morland. He moved to Quinter in 1927 and continued to practice there except for a short time in 1938 when he served in a government position in Missouri and Texas.

Joseph Fowler, M.D.

Dr. Joseph Fowler, 72, a Kansas physician since his graduation from the University Medical College of Kansas City in 1907, died at his home in Osawatomie, October 25. He was an active member of the Miami County Medical Society. Dr. Fowler practiced first in Paola, leaving there in 1916 to move to Fontana. Ten years later he went to Osawatomie and continued to practice there until his death.

George Wightman Kirby, M.D.

A physician who had practiced medicine in Wichita since 1919, Dr. George W. Kirby, 73, died at a hospital there on October 27 after an illness of three weeks. He was graduated from Rush Medical College, Chicago, in 1905 and began practice in Millersburg, Indiana. During World War I he served with the Army in an overseas surgical unit. He was an active member of the Sedgwick County Medical Society.

Arthur Edgar Bence, M.D.

Dr. A. E. Bence, 65, an active member of the Sedgwick County Society, died at his home in Wichita November 19 after a short illness. Dr. Bence, who specialized in orthopedics, had been practicing in Wichita since 1926. He was a graduate of the State University of Iowa College of Medicine with the class of 1921. He was a fellow of the American Academy of Orthopedic Surgeons.

ANNOUNCEMENTS

A six-day postgraduate course entitled "General Practice Review" will be offered at the University of Colorado Medical Center during the week of January 17-22, 1955. A separate area of practice will be presented each day as follows: Monday, medicine; Tuesday, pediatrics; Wednesday, surgery; Thursday, anesthesiology; Friday, obstetrics and gynecology, and Saturday, trauma.

Hotel reservations may be made through the office of Graduate and Postgraduate Medical Education, University of Colorado Medical Center, 4200 East Ninth Avenue, Denver 20, Colorado, until December 20. That office will also supply complete information and programs.

The International Academy of Proctology announces its annual cash prize and certificate of merit award contest for the best unpublished essay on proctology or allied subjects. First prize will be $100. Entries, limited to 5,000 words, must be received no later than February 1, 1955, at the offices of the Academy, 147 Sanford Avenue, Flushing 55, New York.

The Institute of Industrial Health of the University of Cincinnati is now accepting applications for a limited number of fellowships in industrial medicine. Any registered physician who is a graduate of a Class A medical school and who has completed at least two years of training in a hospital accredited by the A.M.A. may apply.

Stipends vary in accordance with the marital status of the individual, from $3,000 to $3,600 the first year to $3,400 to $4,000 in the second year. In the third year the candidate will be compensated for his service by the industry in which he is completing his training.

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Parkinson's Disease

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In 1817, with a certain sense of apology, James Parkinson submitted "An Essay on the Shaking Palsy"[1] for publication. In its preface he says . . . "some conciliatory explanation should be offered for the present publication: in which, it is acknowledged, that mere conjecture takes the place of experiment; and that analogy is the substitute for anatomical examination, the only sure foundation for pathological knowledge. To delay . . . publication did not, indeed, appear to be warrantable. The disease had escaped particular notice; and the task of ascertaining its nature and cause by anatomical investigation, did not seem likely to be taken up by those who, from their abilities and opportunities, were most likely to accomplish it. That these friends to humanity and medical science, who already unveiled to us many of the morbid processes by which health and life is abridged, might be excited to extend their researches to this malady, was much desired; and it was hoped, that this might be procured by the publication of these remarks."

Historically, Parkinson credits Galen with having written of the disease, later Sylvius de la Boe, Juncker, and Cullen. To Parkinson goes first credit for using the term paralysis agitans, and his description of the syndrome is classically as follows: "Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace; the senses and intellects being uninjured."[1]

Parkinson next discussed the natural history and course of this disease in detail. He concluded the first chapter by presenting six case histories. One of these (Case VI) is of special import. This patient was rendered hemiplegic by a cerebral vascular accident, and it was remarked . . . "neither the arm nor the leg of the paralytic side was in the least affected with the tremulous agitation; but as their paralyzed state was removed, the shaking returned." It was this case that later, perhaps, suggested to the neurological surgeon that he might have something to offer to certain patients.

In Chapter III, he gave a differential diagnosis which included palsy due to compression of the brain, alcoholic overindulgence, tea and coffee overindulgence, certain senile tremors, and anomalous cases of convulsive affections. It was his opinion that the pathological lesion was in the cervical portion of the spinal cord, later extended to the medulla oblongata, and that the signs and symptoms observed were due to interruption and irregularity in the direction of the nervous flow. Parkinson was of the opinion that treatment should consist of phlebotomy from the upper part of the neck, followed by application of vesicatories, and appropriate use of a substance to obtain a purulent discharge.

Prior to the appearance of epidemic encephalitis in 1917, Parkinson's disease was by and large a disease of later years, seldom occurring before 40 and usually making its initial appearance between 50 and 60. Cases seen early in life were of enough interest to warrant special reports, and the name of juvenile paralysis agitans was used. The following classification was compiled from a number of sources.

1. Syphilitic—Neill[3] recently reported a case of congenital syphilis in which several typical features of Parkinsonism were seen. Guillain[4] in 1935 and Wilson[5] in 1940 reported cases due to acquired syphilis. The signs may appear soon after the original infection or may be delayed for many years. The syndrome has also been seen in combination with tabes dorsalis and luetic paresis.[3] In Neill's case, improvement was witnessed following treatment with penicillin.

2. Toxic effects of carbon monoxide, manganese, cyanide, and carbon disulfide are all reported as causes of the disease.[6, 7, 8]

3. As a sequel to epidemic encephalitis (encephalitis lethargica, Type A encephalitis, von Economo's encephalitis)—Post-encephalitic Parkinsonism first attracted attention during the epidemic of 1917-1925. Boyd[9] states that around 20 per cent of patients with this type of encephalitis will subsequently exhibit one or more of the features of Parkinsonism. These cases are usually younger, and rigidity is often more prominent than tremor.

4. Arteriosclerotic changes can cause Parkinsonism, and this condition is a distinct and increasingly more common one characterized by an abrupt onset in later life. The tremor is coarse and invariably bilateral. There are often coincident findings which suggest diffuse cerebral arteriopathy (atherosclerosis)

This is one of 11 theses, written by fourth year students at the University of Kansas School of Medicine, selected for publication by the Editorial Board from a group judged to be the best by the faculty at the school.

Thesis written while the author was a fourth year student. Dr. Halliday is now interning at Good Samaritan Hospital, Portland, Oregon.

such as dementia or bulbar dysfunction.[6]

5. "Idiopathic" degenerative paralysis agitans is a progressive degenerative disease of late middle life, characterized classically by tremor, with rigidity being a less prominent feature.

6. Due to acute hemorrhage into the basal ganglia.[8]

7. Due to neoplasms.[8]

8. Due to trauma.[7]

The understanding of the clinical manifestations of Parkinson's disease and any discussion of the pathological lesions is dependent upon a knowledge of the extrapyramidal motor system. This is defined by DeJong[7] as the most highly developed portion of "the old motor system." It is closely allied with the centers of motor integration in the brain stem concerned with regulation of tone and primitive postural and righting reflexes. It is also connected with those portions of the cerebral cortex which have to do with motor control. The nuclear centers of the extrapyramidal system, generally speaking, are situated in the basal ganglia, and Parkinson's disease is frequently referred to as a disease of the basal ganglia or of the striatum. Stated dogmatically, these centers are the caudate and lenticular, the latter being composed of the putamen and globus pallidus.

There are other structures which are functionally and clinically related to the extrapyramidal system. These are the subthalamic nucleus or corpus Luysi, red nucleus, and substantia nigra. In addition, there are extra pyramidal portions of the cerebral cortex—that portion anterior to the premotor area of the frontal cortex and another area in the parietal cortex. The basal ganglia and the related structures constitute an important efferent system. The parts of the cortex mentioned above discharge to the midbrain nuclei, the red nucleus and substantia nigra in part, and these latter structures in turn discharge to the brain stem and the spinal cord.

Although dominated by the cerebral cortex, the "old motor system" has a steadying influence on volitional movements and may be utilized for the initiation and production of many more or less automatic movements. It is these habitual movements of daily life that are most impaired in diseases of the basal ganglia.

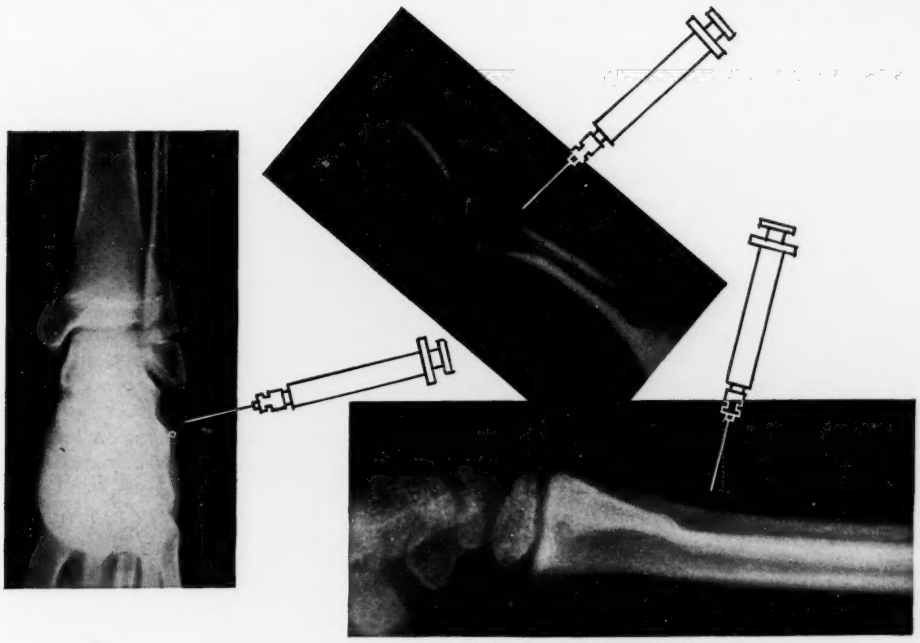
It is generally agreed now that the pathological lesions of Parkinson's disease are in the extrapyramidal motor system. Gower (1888), Omerod (1890), Anton (1895), and Jelgersma (1909) noted changes in the basal ganglia in chorea, athetosis, and paralysis agitans, but the first adequate descriptions of the relationship of neurologic symptoms were made in 1911 and 1912 by Alzheimer, Vogt, Wilson, and Lewy.[7]

Hunt (1917)[10] demonstrated atrophy of the ganglion cells of the globus pallidus in cases of typical Parkinson's disease. Jacob (1925) showed degeneration also of the substantia nigra.[10] Boyd[9] states that the cause of the degeneration is not known and suggests it might be in the form of a senile atrophy, also saying that lesions in post-encephalitic Parkinsonism were found in both the red nucleus and the substantia nigra. Oseki[10] (1924) examined brains from senile patients who had not had Parkinson's disease and saw changes identical with those ascribed to this disease. Oliver[10] mentions that cases have been reported in which the tremor and rigidity were unilateral and the microscopic degenerative changes bilateral.

In general it may be said that disease of the striatum is characterized by some positive and some negative signs and symptoms: (1) general increase of muscle tonus, that is rigidity; (2) abnormal involuntary movements, that is tremor; (3) poverty of voluntary, especially spontaneous movements, namely hypokinesia; (4) impairment of automatic associated movements; (5) absence of "true" paralysis, namely absence of signs of involvement of pyramidal tracts; (6) absence of sensory disturbances.

The signs and symptoms of Parkinson's disease and the general order of their appearance are so aptly described in the original essay[1] that the following is given verbatim: "So slight and nearly imperceptible are the first inroads of this malady, and so extremely slow is its progress, that it rarely happens that the patient can form any recollection of the precise period of its commencement. The first symptoms perceived are, a slight sense of weakness, with a proneness to trembling in some particular part; sometimes in the head, but most commonly in one of the hands or arms. These symptoms gradually increase in the part first affected; and at an uncertain period, but seldom in less than 12 months or more, the morbid influence is felt in some other part. Thus assuming one of the hands and arms to be first attacked, the other, at this period becomes similarly affected.

"After a few more months the patient is found to be less strict than usual in preserving an upright posture; this being most observable whilst walking, but sometimes whilst sitting or standing. Sometime after the appearance of this symptom, and during its slow increase, one of the legs is discovered slightly to tremble, and is also found to suffer fatigue sooner than the leg of the other side; and in a few months this limb becomes agitated by similar tremblings, and suffers a similar loss of power. As time and disease proceed . . . difficulties increase; writing can now be hardly at all accomplished; and reading, from the tremulous motion, accomplished with some difficulty. At this period . . . the patient has recourse to walking, a mode of exercise to which the sufferers from



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this malady are in general partial; owing to their attention being thereby somewhat diverted from their unpleasant feelings . . . but as the malady proceeds, even this temporary mitigation of suffering . . . is denied. The propensity to lean forward becomes invincible, and the patient is thereby forced to step on the toes and fore part of the feet, whilst the upper part of the body is thrown forward as to render it difficult to avoid falling on the face . . . being at the same time, irresistibly impelled to take much quicker and shorter steps, and thereby to adopt unwillingly a running pace.

"In this stage . . . the tremulous motions of the limbs occur during sleep, and augment until they awaken the patient. . . . As the disease proceeds toward its last stage, the trunk is almost permanently bowed, the muscular power is more decidedly diminished, and the tremulous agitation becomes violent. His words are now scarcely intelligible . . . so much are the actions of the muscles of tongue and pharynx impeded . . . another very unpleasant circumstance occurs; the saliva fails of being directed to the back part of the fauces, and hence is continually draining from the mouth . . . the tremulous agitation becomes more vehement. It now seldom leaves him for a moment; . . . the power of articulation is lost. The urine and faeces are passed involuntarily; and at the last, constant sleeplessness, with slight delirium, and other marks of extreme exhaustion, announce the wished-for release."

Perhaps the most significant omission from this masterful description is the waxy, masklike, rigid facies so often seen. To sum up, the salient signs and symptoms are (1) coarse, rhythmic, pill-rolling tremor, usually one of rest, sometimes extending to the tongue and head, (2) plastic muscular rigidity, (3) masklike facies, (4) ante-flexed posture, (5) loss of associated arm movements when walking, and (6) hesitant initiation of walking, with festination, propulsion, retropulsion, or lateropulsion and acceleration. The diagnosis of a fully developed case of Parkinson's disease offers no difficulty.

However, the early diagnosis of this condition is not so easy. This is discussed in detail in a recent article by Wartenberg.[11]

The course of the disease is slow, often lasting 5, 10, or 15 years. Ultimately every patient becomes bedridden and has to be fed and nursed. The prognosis is hopeless and, while the disease itself does not kill, there is no chance of recovery.

The treatment of Parkinson's disease is essentially one or a combination of the following: medical, surgical, by physiotherapy, or by psychotherapy.

The ever-increasing number of drugs introduced and extolled is sufficient indication that none is entirely satisfactory. Certainly there is nothing to even approach the efficacy of cyanocobalamine for pernicious anemia or insulin for diabetes mellitus. Some of the drugs available will give relief and bring about improvement in some patients and not in others; certain of symptoms may be improved and others not. Indeed, there not only are innumerable articles dealing with treatment, there are even articles[12] discussing the hazards and common fallacies present in evaluation of therapeutic results. Extreme divergence of opinion has been characteristic of therapeutic claims since the original paper.

As was mentioned previously, Parkinson used phlebotomy and induced infection for treatment.[1] Charcot suggested horseback riding and eventually devised a contraption in which his patients would sit and be shaken for prescribed periods of time. In 1874,[15] Charcot introduced belladonna therapy in this syndrome. In 1882,[13] Gnauck discovered the effectiveness of hyoscine (scopolamine) in palliation of the symptoms of Parkinson's disease. This opened the present era of medical therapy. Later, other alkaloids of the solanaceous group were noted to have similar effects. These were atropine, hyoscyamine, extracts of the stromonium leaf, and extracts of other plants containing the mydriatic alkaloids.

Through the years, many drugs for both oral or parenteral administration have been tried and have fallen into disuse, such medicaments as quinine, neostigmine bromide, iodides, magnesium sulfate, amphetamine, snake venom, salicylates, and phenobarbital. Vitamins of all types and combinations have had their periods of enthusiastic acceptance but failed to stand the test of time.[16]

Therapy must be individualized, and often trial and error with drug combinations will discover what is most successful for a certain patient. The effective drugs fall essentially into three groups. These are the belladonna or solanaceous drugs, the antispasmodics, and the antihistaminics.

A. THE BELLADONNA GROUP

1. Atropine sulfate in 0.5 per cent solution. This is said to be of special value in the younger age groups and in post-encephalitic cases.[14] The recommended dosage is 10 to 30 drops three times a day. A recent article[17] suggests giving initial doses of three drops at intervals of at least six hours because of slow rate of excretion. The dose is then increased one drop three times a day every three days until a dosage of ten drops three times a day is reached. Excessive dosage may produce vomiting, mental confusion, dizziness, and hallucinations.[17] Other undesirable symptoms are blurring of vision, dryness of skin and mucous membranes, somnolence, and tachycardia.[18]

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useful preparations, especially in reducing tremor and excitement.[14] The dose is 0.25 to 0.6 milligrams two to three times a day. Signs of toxicity are generally the same as those given for atropine.

3. Tincture of stramonium has been employed for years to control rigidity and tremor. The effect upon rigidity is less than that obtained with some of the newer preparations as a general rule. The tincture is prescribed in doses of 10 to 20 drops three times a day or, in the tablets, in two-grain dosage three times a day.[14] According to some,[17] this drug is easily tolerated by the elderly.

4. Rabellon (Sharpe and Dohme) is a compound of belladonna alkaloids containing 0.5 mg. of atropine and hyoscyamine with traces of scopolamine. It is given in one-half, one-fourth, or full tablets two, three, or four times a day. Although a good muscle relaxant, Rabellon has little action against tremor.[17]

5. Vinobel, which is dispensed in tablets containing 0.4 mg. of the active alkaloids for elderly patients and 0.8 mg. for young persons, is an effective antispasmodic.[14, 17] Side reactions are those of the other belladonna products.

6. Bellabulgara is prepared in tablets containing 0.45 mg. of the alkaloids atropine and hyoscyamine and a trace of scopolamine.[17] In the late 1930's and early 1940's, this preparation was in particular vogue.[15] It was thought at this time that it possessed some particularly efficacious properties. It is administered in one-half or full tablet doses three times a day.

B. THE SYNTHETIC ANTISPASMODIC DRUGS

1. Artane (Trihexiphenidyl) is manufactured by Lederle Company. It is perhaps the most important recent addition to the drugs used for Parkinson's disease. Pharmacologically, Artane exerts both atropine-like and antihistaminic effects.[19, 22] On isolated intestine loops, its relaxant action is half that of atropine.[19] It is mildly excitant to the central nervous system but much less so than atropine.[19] It is one per cent as potent a vagus inhibitor as atropine.[22] Salivation is but slightly inhibited.[19]

A recent article[17] stated that Artane is recommended as the basic drug in treatment of all new cases. It may be used at all age levels.[17] Its chief advantage over the traditional belladonna drugs is in the wider margin of safety existing between the effective and toxic doses. Another advantage is that Artane doses need not be continuously increased in order to maintain its action.[19] It may be safely used in patients with cardiac disease, hypertension, hepatic or renal disease.[14, 22] It had no ill effects upon blood pressure, respiration, blood count, renal or hepatic function, sugar metabolism, growth, and reproduction in laboratory animals over a six-months period.[22]

The first six reports[20] in the literature appeared in 1949 and 1950. Each was a large series, and combined results listed improvement in 76 per cent of cases. They reported Artane to be most effective in controlling rigidity and spasticity with 10 per cent incidence of mild side reactions and 4 per cent incidence of severe side reactions. The patient should be started on 1 mg. each day. This is increased 1 or 2 mg. each day to a total of 6 to 10 mg., which is divided into three or four doses.

2. Curare (placed in this group for convenience) was tried about 1927 and abandoned.[21]

3. Diparcol is a synthetic antispasmodic developed in France. Results with it were not too satisfactory. Its manufacture has been discontinued because of its toxic manifestations and occasional cases of agranulocytosis.[6]

4. Tolserol (Myanesin, Mephanesin) is given first as one 250 mg. tablet three times a day and rapidly increased to three, four, or five tablets three or four times a day.[22] One group[22] used Tolserol in 22 patients and had to discontinue it in all but one because of nausea, precordial discomfort, and pronounced increase of tremor.

5. Panparnit (Carmiphen hydrochloride) was developed in Switzerland. Results have not been good, and a high incidence of severe toxic effects is reported.[14, 22]

6. Parsidol comes in 50 mg. tablets. It is administered in one-half tablet doses four times a day to elderly patients and full tablets four times a day to younger persons. Results so far have been poor.

C. THE ANTIHISTAMINICS

1. Benadryl. It was appreciated by early investigators that the anticholinergic activity of antihistamine substances might be of value in the therapy of Parkinson's disease. The use of such substances began with the treatment of four patients as a part of a routine screening of Benadryl in many diseases.[23]

Budnitz,[24] in 1948, released a preliminary report concerning eight patients suffering with Parkinson's disease who were treated with Benadryl. He observed that "all of them in the arteriosclerotic group were treated with Benadryl over a period varying from 3 to 14 months. All patients noted considerable improvement in the symptoms as long as the drug was administered. Four of the patients treated continued to use parasympathetic inhibitory drugs of the atropine series, and there seemed to be a synergistic action between these drugs and Benadryl."

Moore[25] reported a series of 52 patients using Benadryl and Benadryl and hyoscine. He stated that

WHEN SYMPTOMS ARE DISTRESSING BUT DISGUISED . . .

"It is strange," Malleson says, "how little clinical recognition" has been given to the "negative behavior" or "endogenous misery" of the woman with endocrine imbalance. Largely accountable for this, of course, is the patient's own reluctance to discuss these symptoms with her physician until she actually suffers from some of the more obvious menopausal symptoms such as hot flushes. Even then she may become so accustomed to her change in feeling she can't remember what it's like to feel well.[1]

Changes in the mood pattern are just a few of the many distressing symptoms of declining ovarian function which are so often disguised because they do not always coincide with cessation of menstruation, and at times will occur long before, and even years after. Other good examples are insomnia, headache, easy fatigability, arthralgia — and understandably so, when one considers that the loss of ovarian hormone "withdraws one of the most important metabolic regulators of the organism."[2]

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his patients did not fare well on Benadryl alone but showed marked improvement on Benadryl plus a member of the atropine group. Twenty-five per cent of his patients had drowsiness which was eliminated when amphetamine was administered upon arising and at noon. This was the only distressing side effect noted.

At present, Benadryl is one of the most often used preparations. In a recent article,[17] it was stated that Benadryl controls tremor well, allays tension and excitement, and aids patients with insomnia. Side reactions of somnolence and fogginess may so disturb elderly patients as to limit use to bedtime. Usually 50 mg. doses are given two to four times daily. Bercel[26] states that of the various symptoms of Parkinsonism, subjective complaints due to vegetative nervous system dysfunction—muscle cramps, rigidity, diaphoresis, sialorrhea, asthenia, emotional incontinence, and tremor—were most favorably affected. He also stated that a six-weeks trial was necessary for evaluation.

2. Thephorin is perhaps the second antihistaminic which should be mentioned. Cohen and Criep[27] state that a few months before the first articles about Benadryl and Parkinsonism appeared, they had noticed considerable symptomatic improvement in a patient with Parkinson's disease who was receiving Thephorin for coexisting allergic rhinitis. They conducted a series using Benadryl, Pyribenzamine, and Thephorin. They stated that Thephorin resulted in the greatest degree of improvement with tremor, hypertonicity, and rigidity being most frequently benefited. The dosage recommended is 25 mg. two or three times a day.

3. Pyribenzamine has not been of value in treatment of Parkinson's disease.[13, 27]

4. Histadyl was reported to elicit poor results.[13]

Hand[14] states that Benadryl and Thephorin are the only antihistaminics of value in Parkinson's disease. These agents are perhaps synergistic with Artane; by the trial and error method, some combination of the three above discussed groups of drugs should be found which will afford a degree of palliation for the sufferer.

Parkinson's Case VI, in whom temporary unilateral cessation of symptoms was observed following a cerebral vascular accident, was evidence that destructive neurosurgical procedure might have a place in the treatment of selected cases.

A recent monograph by Oliver[10] discusses this aspect of treatment in adequate detail. Of slightly more than 1000 patients examined, 300 were admitted for further hospital study, and 93 eventually were selected for operation. He noted that no abnormalities in spinal fluid examination were discovered. Also, the scalp leads from an electroencephalograph revealed no unusual characteristics. Fifty cases were studied by pneumoencephalograms, and no convincing abnormality was observed.

Numerous operations have been proposed. Essentially all are alike in that the corticospinal tracts are sectioned at some point in their descent. The operations differ as to the site selected, cortex or cervical cord, and the depth to which the scalpel is pushed. It would seem, in a certain small percentage of cases in which tremor is unilateral, that surgery might be of value. The vast majority of patients with Parkinson's disease will be in the older age groups. Special efforts should, therefore, be directed toward being as certain as possible that the patient can tolerate surgery.

Physiotherapy should be confined to increasing muscle tone rather than to providing momentary comfort to the patient.[17] It should consist of massage, stretching of muscles, and active exercise with special equipment.[17] Heat lamps, diathermy, and ultraviolet machines are of little value. Physiotherapy, if enthusiastically administered, will always produce some improvement. An occasional short course of active exercises from a physiotherapist with an energetic and optimistic approach may sometimes help these patients make full use of any persisting potential capacity for physical activity.[6]

As in the treatment of most diseases, psychotherapy is of value in Parkinson's disease. Psychotherapy is perhaps no more than a conscious effort to maintain a good doctor-patient relationship. It is that sort of common-sense encouragement and reassurance which every physician is called upon to provide every day.

Quite naturally, many with this disease tend to become sorry for themselves, and they need to be protected from the over-sympathy which they receive from their friends and families and to be encouraged to keep going as long as possible. They are also prone to consider their disability as more conspicuous than it really is. The most important factor is undoubtedly to try to maintain the patient's morale, and Parkinsonism is one of several incurable chronic diseases of the nervous system in which the most effective treatment is psychotherapy in its least specialized sense, administered consciously or unconsciously by an understanding practitioner.

Parkinson's disease, known for centuries but first described by James Parkinson in 1817, is a slowly progressive affection of the central nervous system. It can be caused by arteriosclerosis, encephalitis lethargica with an interval of several years before symptoms appear, syphilis, carbon monoxide, carbon disulfide, manganese, hemorrhage, trauma, or neoplasm, or it may be of the so-called idiopathic type. The signs and symptoms are discussed with an attempt to correlate the clinical findings with the altered physiology of the extrapyramidal system.

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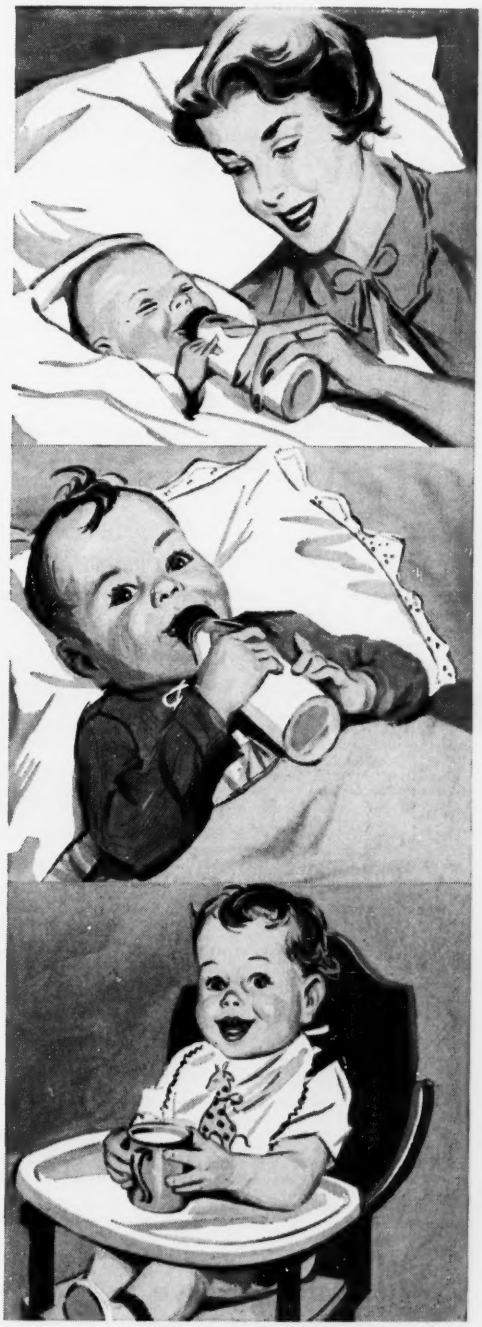

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Although there is no cure for the disease, therapy can and should be actively and energetically undertaken by the physician. Therapy was discussed as medical, surgical, physiotherapeutic, and psychotherapeutic. Artane and Benadryl are probably the most efficacious drugs available. It was stressed that combination therapy be used until the most improvement is noted. An occasional patient may be a candidate for surgery, and the criteria for this are discussed. Physiotherapy is of limited value. Of perhaps the most value is the commonsense psychotherapy which every physician can employ if he will. The patient should be urged and encouraged to remain as active as his disabilities allow.

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BOOK REVIEWS

A History of Medicine, Volumes 1 and 2. By Ralph H. Major. Published by Charles C Thomas, Springfield, Illinois. 1155 pages. Price $14.50.

In the preface Dr. Major defines the purpose and scope of his work. "This book is not written for the specialist in medical history, to whom most of the facts related are already well known. It is written primarily for the medical student and the medical practitioner, in an attempt to interest them more in the history of their own profession, which, despite attacks and abuse, despite quacks and charlatans, and in spite of its own mistakes, has proved itself more enduring than any of the civilizations which gave birth to it.

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It is a readable book beautifully printed on fine paper. *A History of Medicine* will be of interest to the medical student and the medical practitioner. It will be a popular source reference in every library, but it has a wider potential influence than in professional circles.

The author uses the historian's dispassionate approach, but his subject is filled with the breathless suspense of discovery, the terror of plagues, and the comfort of continual progress. It is science, but the science of humanity. It is history, but more vital than the conquest of armies. It is fact, but the fact of living, personal experience.

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Galen of Pergamon. By George Sarton. Published by University of Kansas Press, Lawrence, Kansas. 112 pages. Price $2.50

Galen of Pergamon is the third volume in the Logan Clendenning Lectures on the History and Philosophy of Medicine to be published by the University of Kansas Press.

This is the readable account of the life of the famous and influential physician and makes for excellent bedside reading for every physician. Most of the physicians in Kansas have visited the Library of the History of Medicine and know that the Logan Clendenning Library is one of the great libraries of medical history in the world. Those who were not fortunate enough to hear Dr. Sarton present the material covered in the book will welcome this fine volume.—*W.L.V.*

Manual of Clinical Mycology, Second Edition. By Norman F. Conant, David T. Smith, Roger D. Baker, Jasper L. Callaway, Donald S. Martin. Published by W. B. Saunders Company, Philadelphia. 456 pages, 202 figures. Price $6.50.

This manual contains a concise description of the several recognized mycotic diseases together with discussion of epidemiology, diagnostic methods, and treatment. The sections on laboratory diagnosis are sufficiently detailed to serve as a reference, and a brief chapter on general mycology is included for orientation. There are numerous excellent photographs of lesions, x-rays, and microscopic preparations. Each chapter concludes with a comprehensive bibliography.

This edition has been revised to include the rather large amount of information accumulated in the last 10 years, especially about the systemic fungus infections.—*H.R.*

Urology, Volumes I, II, III. By Meredith Campbell with 51 Contributing Authorities. Published by W. B. Saunders Company, Philadelphia. 2,356 pages, 1,148 figures. Price $60.

Many excellent textbooks of urology have been published since 1900 when urology became an accepted surgical specialty, and this new study edited by Dr. Campbell is one of the best. In 1926 Saunders published a similar set of volumes edited by the late Dr. Hugh Young which for many years was a standard textbook in urology. Twenty-eight years later this new text written by competent authors will again become a definitive reference text in urology.

The collaborating authors are all outstanding, and their contributions bring up-to-date the many developments of the last few years. An excellent integration with the basic sciences is achieved by the use of monographs by Doctors Pitts, Huggins, Moore, Ash, Engle, Hotchkiss, Jenkins, and others. Related fields are also covered by authorities. The field of urology has been greatly enriched by this splendid effort.—*W.L.V.*

Clinical Management of Behavior Disorders in Children. By Harry Bakwin and Ruth Morris Bakwin. Published by W. B. Saunders Company, Philadelphia. 495 pages, 14 figures. Price $10.

The authors of this book have succeeded in doing what has long been needed. They have gathered together in one book an extremely readable guide and reference book for the use of the general practitioner and pediatrician who must handle the great bulk of the behavior and emotional problems of children and often must be the source of referral for more specialized services. This book is also a valuable source of reference for the child psychiatrist and members of ancillary disciplines because of the ready availability of certain statistical information.

The book is rich in references to and abstracts from recent significant literature, and it is often from these abstracts that the above mentioned statistical material is taken. For example, in discussing cerebral palsy, McIntire's article on the subject is referred to, and his list of the frequency of the various etiological factors in cerebral palsy is cited. Another example of the useful information to which one might have need to refer frequently is the table setting forth the percentage of epileptics engaged in various occupations. Still another example is found in the chapter on sex education in which one finds a book list on sex education, books for children and adolescents or their parents.

Among the general attributes of the book should be mentioned the 34 pages of index which make for easy reference to specific topics.

The authors have included as their first section an excellent discussion of growth and development in which emphasis is placed on the emotional development of the child. The motor and mental capabilities at a given age are also adequately discussed.

The second section of the book takes up a discussion of general psychologic care from the newborn period through adolescence. The authors' point of view in regard to most matters of training, including early feeding techniques, is one of down to earth practicality with a notable absence of any rigidity.

The third section on the care of the physically ill and handicapped child takes up such matters as hospital care of children. The authors advise home care

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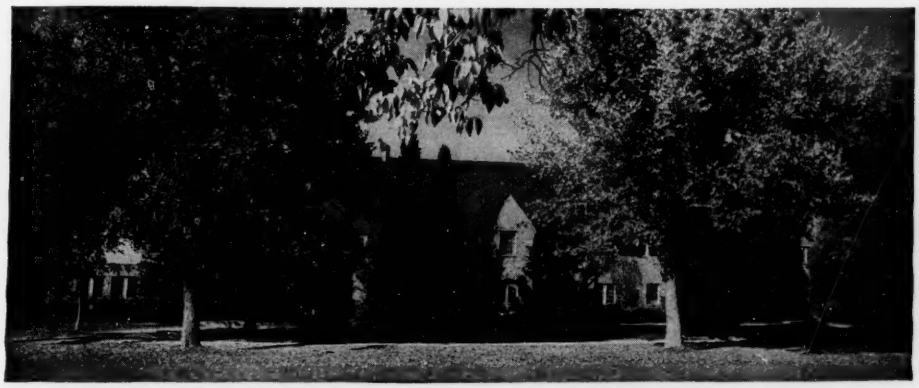

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Two sections on the problems related to mental functioning and developmental abnormalities should give invaluable aid to the practitioner confronted with these problems in his practice, and they should serve also as a source of information and ideas should the practitioner be called upon to give talks to lay groups.

The sections on problems related to emotional development include chapters on abnormal emotional states, sex problems, and emotional deprivation in infants. Sections on problems of habit and training, organic disturbances with a large psychic component such as asthma, skin diseases and ulcerative colitis, anti-social behavior, and more specific syndromes such as schizophrenia in children are to be found in this book.

In general there is little to criticize, and the basic theoretical concepts and procedures are in line with current psychiatric thinking.

Last, but certainly not the least of the good features of this volume, is the list of references which follows each chapter.—*R.A.M.*

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The fact that a man who earns $4,500 a year spends more than 2½ hours each day earning enough to pay his taxes, federal, state, and local, was one of the surprising statistics developed by the California Taxpayers Association in a recent survey. The private research organization made an analysis of the 90 billion dollars being collected by governmental agencies this year.

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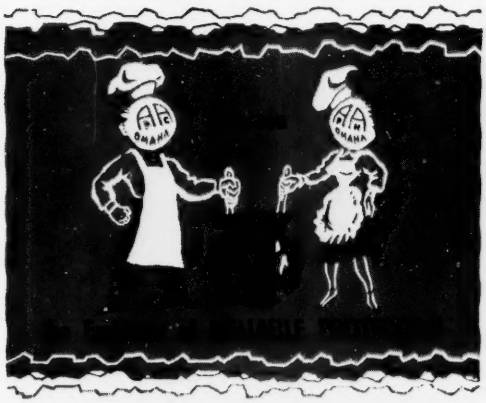

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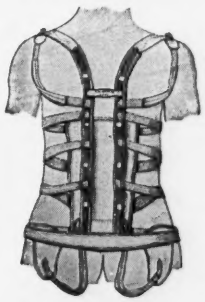

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Obstetricians Meet

A meeting of the Kansas State Obstetrical Society was held at the Muehlebach Hotel, Kansas City, on October 9, at the time of the refresher course in obstetrics at the University of Kansas Medical Center. Wives of members were guests. Dr. J. Curtis Lund of Rochester University was speaker of the evening.

Manual on Nursing Activities

A new manual designed to aid hospitals in making better use of personnel, *How to Study Nursing Activities in a Patient Unit,* was recently published by the Public Health Service, Department of Health, Education, and Welfare. The publication offers a method by which hospitals of all sizes may determine how nursing personnel time is distributed between duties requiring nursing skills and those which could be performed by other hospital personnel.

The purpose of the study is to give nurses more time to be with patients. Nursing personnel themselves have an opportunity to take part in the study and to analyze their own activities.

The foreword of the manual, written by Dr. Edwin L. Crosby of the American Hospital Association, states, "If many hours of nurses' time are being directed from their true purpose and spent in work others can do, this trend must be corrected. The problem is how to conserve professional nursing skills for their highest use. . . . Any hospital, large or small, can use the manual, adapting it readily to individual needs."

Copies of the booklet may be purchased from the Superintendent of Documents, Government Printing Office, Washington 25, D. C., at 25 cents each.

Rural Health Meeting

The 10th National Rural Health Conference sponsored by the American Medical Association will be held at the Schroeder Hotel, Milwaukee, February 24-26. Discussions will be held on the work of medical society rural health committees, responsibilities of citizenship, and training for rural practice.

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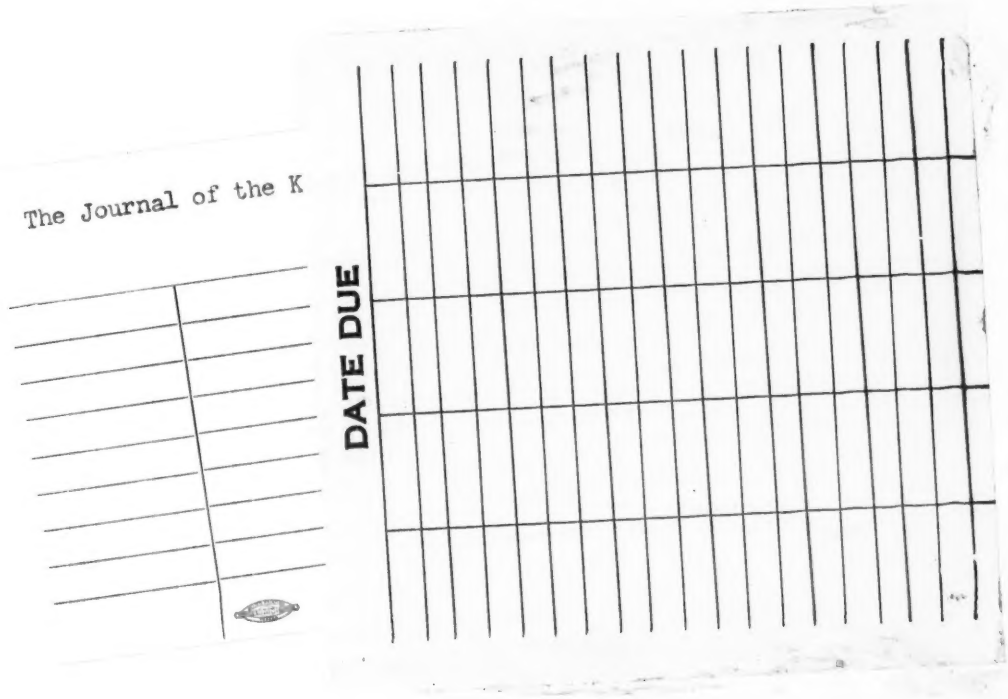
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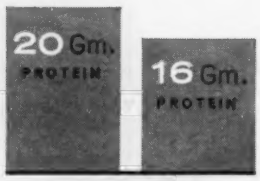

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1. Jeans, P. C., in A.M.A. Handbook of Nutrition, Philadelphia, Blakiston, 1951, pp. 275-298. 2. Stare, F. J., and Davidson, C. S., in The Proteins, American Medical Association, 1945.

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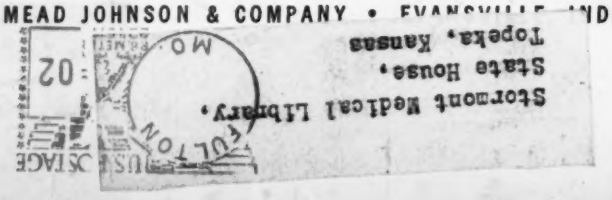
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